The Journal of Thoracic Surgery

VOL. 32 NOVEMBER, 1956 NO. 5

Surgical Forum Issue

A SIMPLE SURGICAL METHOD FOR THE CORRECTION OF MITRAL REGURGITATION USING THE FINGER RING VALVE ELEVATOR

ARAN S. JOHNSON, M.D. (BY INVITATION)
GROSSE POINTE, MICH.

ONE of the problems facing the cardiac surgeon is the development of a simple surgical method for correcting mitral regurgitation. Various techniques have been described recently, but the surgical treatment still remains physiologically unsatisfactory.

PATHOLOGY OF MITRAL REGURGITATION

Upon careful gross examination of one hundred necropsy specimens of hearts with residual rheumatic mitral valvular lesions, the regurgitant defects were found constantly in the posterior leaflet of 70 per cent of the hearts with combined lesions (stenosis and insufficiency) and those with purely insufficient valves. The chordae tendineae in the area of leaflet deformity were shortened and thickened. The edge of the involved leaflet was hyalinized, calcified, and curled under.

METHODS OF DEMONSTRATING DEFECTS

Using the hydrodynamic technique, the presence of an existing physiologic defect can be easily and accurately located by palpation and direct vision: (a) with a finger in the left atrium and water under pressure in the left ventricle, the regurgitant jet is palpable; (b) by excising the left auricular appendage of the necropsy specimen, a more accurate localization of the mitral defect can be made by direct vision. A jet of water can be seen squirting through the defective leaflet whenever present, using the water under pressure technique.

From the Department of Surgery (Cardiovascular), Bon Secours Hosp., Grosse Pointe, Michigan.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

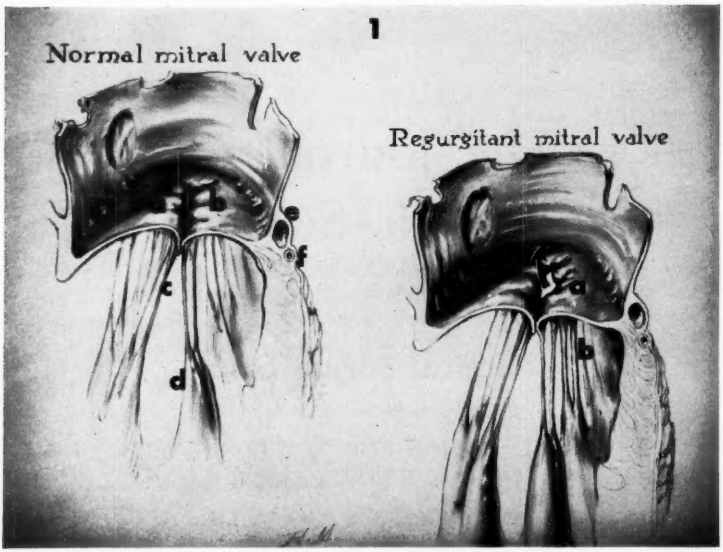


Fig. 1.—Left: Normal mitral valve. *a*, Anterior leaflet. *b*, Posterior leaflet. *c*, Chordae tendineae. *d*, Papillary muscles. *e*, Coronary sinus. *f*, Left circumflex coronary artery.

Right: Regurgitant mitral valve. *a*, Area of defect edge of the posterior leaflet. *b*, Shortened and thickened chordae tendineae in the area of defective valve.

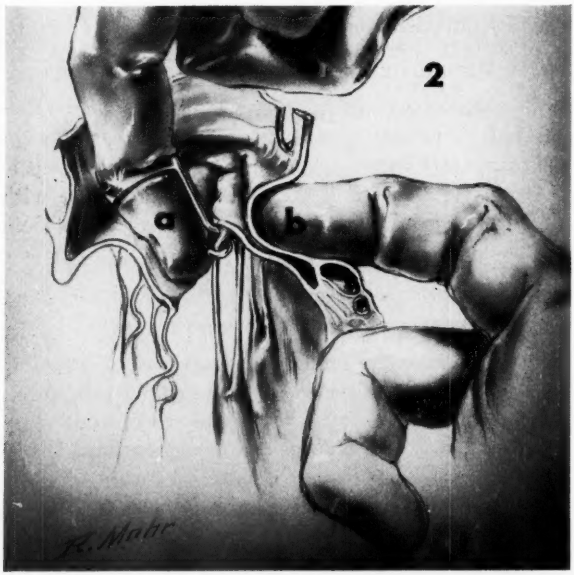


Fig. 2.—The first surgical step in correcting the regurgitation. *a*, Index finger with the ring valve elevator placed around the chordae tendineae at point of insertion into the valve. *b*, Assistant's finger invaginating the posterior atrial wall toward the internally elevated lip of the posterior mitral leaflet.

SURGICAL METHOD OF TREATMENT

Based upon the knowledge that approximately 70 per cent of the mitral lesions are located in the posterior leaflet, a simple surgical method for the correction was designed. The valve is first explored with the index finger of the left hand. If the defect is palpated and localized in the posterior leaflet, the exploring finger is withdrawn. The ring (hook) elevator is then fitted onto the index finger of the left hand and reinserted into the left atrium. The hook end of the ring is placed around the chordae tendineae in the valve area where the edge of the posterior leaflet is curled under. The edge of the curled

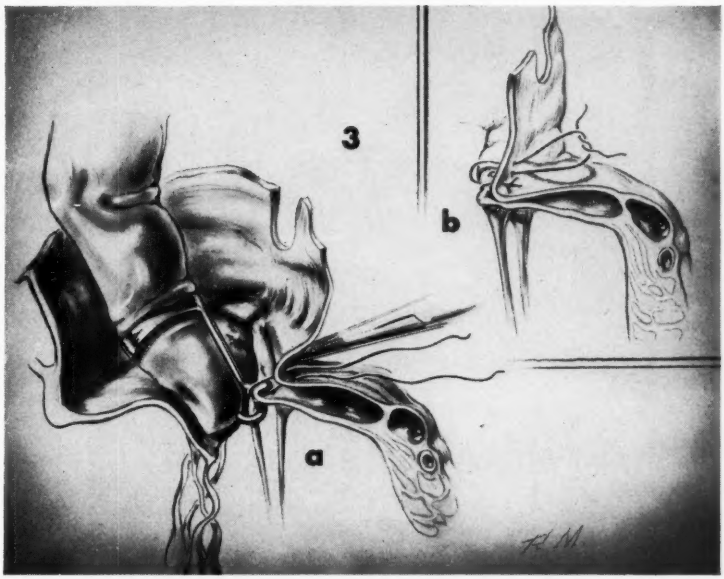


Fig. 3.—The second surgical step in repairing the regurgitant valve. *a*, Placing the first row of silk sutures fixing the edge of the valve to the posterior atrial wall. *b*, Sutures being tied in place.

lip of the valve is then elevated toward the posterior wall of the atrium by stretching the chordae tendineae. The assistant with his finger or a curved Kelly forcep invaginates the posterior atrial wall toward the internally elevated posterior mitral leaflet. Two to three interrupted No. 2-0 silk sutures fix the edge of the defective leaflet to the posterior wall (Figs. 1-4). A second row of interrupted silk sutures is next placed to take the tension off the first row of sutures. A reinforced posterior mitral leaflet has now been constructed. It is semirigid as far as flexibility is concerned. The anterior and medial mitral leaflets become the only freely moving parts of the valve. The mitral valve has now been made physiologically competent. The regurgitant jet is completely absent as a result of a newly reconstructed posterior mitral

leaflet. This technique has been tried and tested many times in the experiments in which hearts with residual rheumatic deformities encountered at necropsy were used.

The surgical technique for the correction of incompetent mitral valves as described can be used for the "blind cardiovalvoplasty" and is equally successful for the "open cardiovalvoplasty" when a mechanical heart pump-oxygenator is employed to by-pass the left side of the heart. The surgical steps for the correction of existing valvular incompetence remain the same when the "blind" or "open" techniques for approaching this problem are employed.

Fig. 4.—The third and final surgical step in repairing the regurgitant valve. *a*, Reinforced and reconstructed posterior leaflet. *b*, Second row of interrupted silk sutures.

CLINICAL APPLICATION

Clinically the finger ring valve elevator has been successfully tried in 6 cases. Three of the patients had the combined mitral lesions (stenosis and regurgitation). These patients obtained excellent results. Of the remaining 3 patients who had pure mitral regurgitation, 2 showed good clinical improvement and the third obtained only fair results. One patient with tricuspid regurgitation was also operated upon. The valve was only partially repaired during the operation with only temporary improvement. A detailed report on these clinically tested cases is being prepared for later publication.

SUMMARY

1. Description of a simple surgical method using the finger ring valve elevator for correcting mitral regurgitation is presented.

2. The clinical application of the surgical technique is briefly discussed.

REFERENCES

1. Benichoux, R., and Chalnot, P.: A Method for the Surgical Correction of Mitral Insufficiency, J. THORACIC SURG. **30**: 148, 1955.
2. Templeton, J. R., III, and Gibbon, J. H., Jr.: Experimental Reconstruction of Cardiac Valves by Venous and Pericardial Grafts, Ann. Surg. **129**: 161, 1949.
3. Bailey, C. P., Jamison, W. L., Bakst, A. E., Bolton, H. E., Nichols, H. T., and Gemeinhardt, W.: The Surgical Correction of Mitral Insufficiency by the Use of Pericardial Grafts, J. THORACIC SURG. **28**: 551, 1954.
4. Harken, D. E., Black, H., Ellis, L. B., and Dexter, L.: The Surgical Correction of Mitral Insufficiency, J. THORACIC SURG. **28**: 604, 1954.
5. Carter, M. G., Gould, J. M., and Mann, B. F., Jr.: Surgical Treatment of Mitral Insufficiency, J. THORACIC SURG. **26**: 574, 1953.
6. Davila, J. C., Mattson, W. W., Jr., O'Neil, T. J. E., and Glover, R. P.: A Method for Surgical Correction of Mitral Insufficiency, Surg., Gynec. & Obst. **98**: 407, 1954.
7. Kay, E. B., and Cross, F. S.: Surgical Treatment of Mitral Insufficiency, J. THORACIC SURG. **29**: 618, 1955.
8. Albanese, A. R.: Posterior Atriocommissuropexy for Surgical Treatment of Mitral Insufficiency, Henry Ford Hospital, International Symposium on Cardiovascular Surgery, 262, 1955.

FURTHER EXPERIENCES WITH THE METHOD OF CONTROLLED UNILATERAL PULMONARY ARTERY OCCLUSION IN THE STUDY OF LUNG FUNCTION

PAUL NEMIR, JR., M.D., H. H. STONE, M.D. (BY INVITATION),
H. R. HAWTHORNE, M.D. (BY INVITATION), AND
T. N. MACKRELL, M.D. (BY INVITATION)
PHILADELPHIA, PA.

IN 1951, Carlens, Hanson, and Nordenström[1] published the first report on unilateral occlusion of the pulmonary artery in dog and man, utilizing a double lumen, balloon-tipped cardiac catheter. In 1953, a preliminary report on the use of this method in the study of lung function was made by us.[2] In the five years since the original report of Carlens and his associates, the number of cases which have been studied by the Stockholm group,[3, 4] Sloan and his associates at the University of Michigan,[5] Brofman and his associates in Cleveland,[6, 7] and in our own series has become sufficiently large so that definitive conclusions may now be drawn from this method of investigation.

The purpose of this report is to give the results of our continuing experience with this method and, second, to attempt to evaluate the present status of the study in the light of the collected series. Bagger, Carlens, Hanson, Malmstrom and Uggla have recently reported detailed studies on 109 patients, and more recently the number of cases studied by these investigators is now over 150, and there has been no serious accident.[8] Sloan and his associates reported studies on 18 patients at this meeting one year ago, and they have now studied over 25 patitents.[9] Brofman and his associates[7] have now performed studies on approximately 100 patients, with particular emphasis not only on pulmonary function study, but also on the study of pulmonary hemodynamics.

PRESENT SERIES

Unilateral pulmonary artery occlusion has now been carried out by us in 35 patients. In five instances, passage of the catheter into the desired branch of the main pulmonary artery could not be accomplished. In 4 of these cases, the cause was apparent at operation, in that the pulmonary artery or the superior vena cava was either compressed or distorted by metastatic carcinoma in the mediastinum. In the fifth case, no apparent cause for the failure could be found. In the group of 35 patients in whom studies were carried out, 27 had carcinoma of the lung, 4 had inflammatory pulmonary lesions, 2 had bronchiec-

From the Harrison Department of Surgical Research, the Department of Surgery, and the Hospital of the Graduate School of Medicine of the University of Pennsylvania, Philadelphia, Pa.

Aided by grants from the Wilson C. Laucks Memorial Foundation, the A. Atwater Kent Fund, and the National Heart Institute of the National Institutes of Health of the U. S. Public Health Service, Grant H1282(c)2.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

tasis, one had a large right upper lobe cavity of undetermined etiology, and one had berylliosis and severe rheumatic heart disease. The youngest patient studied was 37 years of age and the oldest was 73 years of age, with an average age of 61 years. With only a few exceptions, all were patients with poor or borderline pulmonary reserve or associated cardiovascular abnormalities.

METHODS

The procedure used was essentially that as previously stated in the first published article.[2] However, with our continuing experience, changes in technique have occurred with some alterations and refinements. In the earlier experiments, we used a double lumen catheter with the recording lumen either proximal or

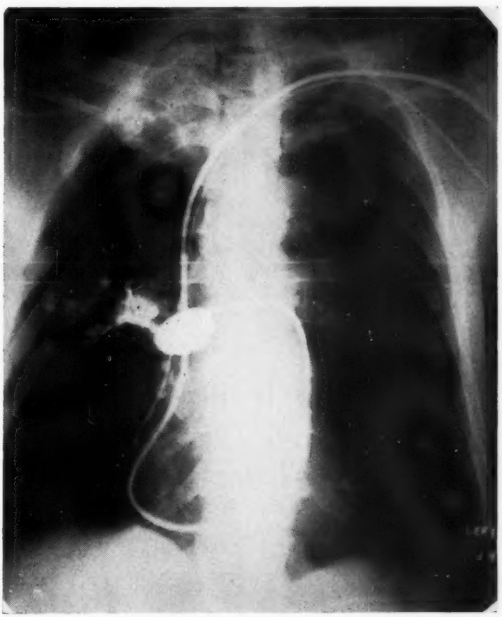


Fig. 1.—Roentgenogram of chest of a 66-year-old man with a large right upper lobe cavity. This patient was studied early in the series and two catheters were passed; the double lumen balloon-tipped catheter has a recording orifice distal to the balloon. The second conventional cardiac catheter is in the pulmonary conus. Ten milliliters of 35 per cent Diodrast was injected distal to the occluding balloon approximately four minutes prior to this roentgenogram. The pulmonary radicals distal to the occlusion were beautifully demonstrated under the fluoroscope immediately after injection, but were less well defined by the time the above roentgenogram could be made.

distal to the occluding balloon. With this type of catheter, it was necessary to pass a second regular cardiac catheter into the pulmonary conus when pressure recordings both proximal and distal to the balloon were wanted (Fig. 1). Recently, however, we have been using a 125 cm. triple lumen cardiac catheter with recording lumina both proximal and distal to the balloon (Fig. 2).* The use of this single catheter has greatly facilitated the procedure (Fig. 3). In the

*Obtained from U.S. Catheter and Instrument Corporation, Glens Falls, N. Y.

earlier cases, it was at times very difficult to place the catheter selectively in the right or left pulmonary artery. As we have gained more experience, however, this is much more readily accomplished. Catheterization of the right or left artery, selectively, has usually taken from ten minutes to one hour and fifteen minutes. In the last 10 cases, using the triple lumen catheter, successful placement has not taken longer than twenty minutes. In the earlier cases, 50 mg. of heparin was given as soon as the catheter was placed in the correct position. However, this practice is no longer felt to be necessary and we have had no difficulty with clotting. Once the cardiac catheter is in position and recording, the femoral artery is rapidly cannulated. All four channels of the Poly Viso electromanometer are thus utilized—one for the continuous electrocardio-

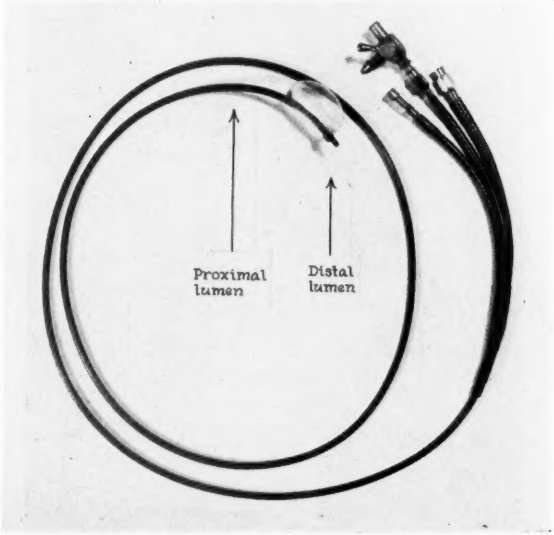


Fig. 2.—Triple lumen, 125 cm., No. 10½ cardiac catheter with recording lumina both proximal and distal to the occluding balloon.

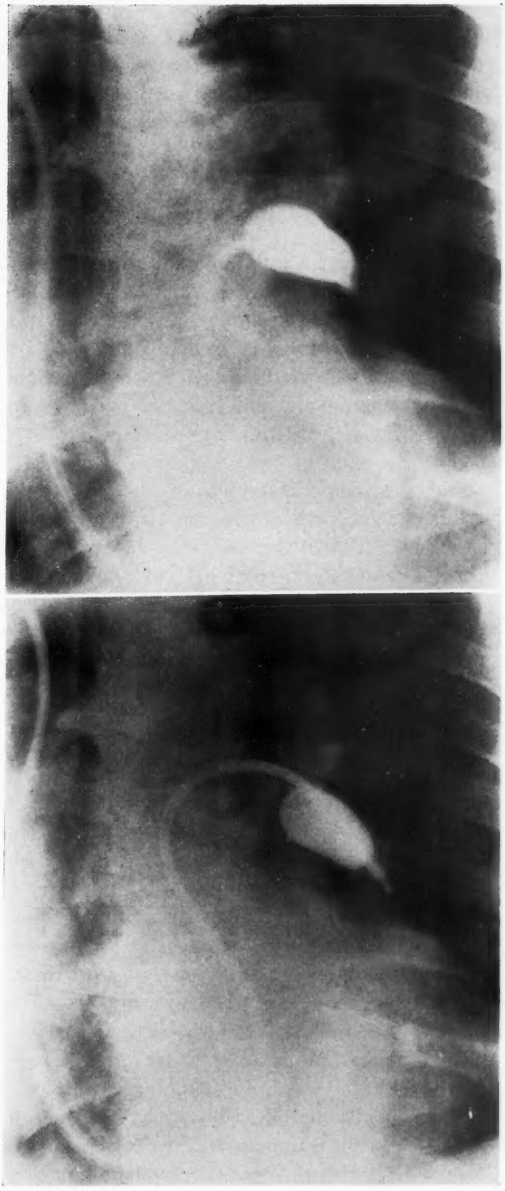
graphic tracing, one for pulmonary artery pressures proximal to the balloon, one for pulmonary artery pressures distal to the balloon, and one for continuous femoral artery pressures. With the catheter in position, occlusion of the artery could be carried out at will.

We have abandoned occlusion of the corresponding main-stem bronchus with the Carlens-Stille endotracheal catheter, since we have not felt that this procedure gave us any significant information by the methods used.

Technical Difficulties Encountered With the Method.—

1. As previously stated, passage of the catheter into the desired position has been, at times, difficult. The double and triple lumen catheters cannot be manipulated with the same ease as the ordinary single lumen cardiac catheter. The triple lumen catheter is a No. 10½ cardiac catheter and it has a recording

A.



B.

Fig. 3.—Roentgenogram of chest of a 73-year-old man with a carcinoma of the lung. The triple lumen catheter is in the left pulmonary artery. Nine milliliters of Diodrast was used to inflate the balloon before complete occlusion was obtained as evidenced by the change in the contour of the distal tracing, the change in pressure, and the alteration of the gas analyses (see Fig 6).

A, Catheter in left pulmonary artery. *B*, Catheter in lobar artery.

lumen both proximal and distal to the occluding balloon. With the use of this catheter we have been enabled not only to record pressure and obtain blood samples for gas analyses both proximal and distal to the inflated balloon, but also to inject substances distal to the inflated balloon. The occurrence of extra systoles, as the large catheter impinges on the right ventricular wall, is almost an invariable accompaniment. However, these arrythmias will disappear immediately upon moving the tip of the catheter. Further mention is made of this.

2. While the balloon could be inflated with ease with the use of 35 per cent Diodrast, withdrawal of the Diodrast when it was desired to deflate the balloon was at times painfully slow, though always accomplished. Between 6 to 10 ml. of 35 per cent Diodrast was used to inflate the balloon. Perhaps the use of Umbradil or Urokon would be better when roentgenograms are desired. If roentgenograms are not desired, inflation is accomplished with saline solution and it may be easily withdrawn.

Complications.—

1. An elevation of the temperature within one to three hours after conclusion of the procedure has occurred in approximately 75 to 80 per cent of the cases. Chills have occasionally preceded the temperature rise. Usually the temperature elevation has been in the range of 101° to 102° F. but on two occasions has been 105° F. In almost all instances, the temperature has returned to normal in one to four hours, and this complication has not been a serious problem. The cause for the temperature elevation is not immediately apparent. Blood cultures have been negative and strict aseptic technique has been employed. Pyrogens in the infusion fluid may have been responsible but this reaction has not generally occurred after routine cardiac catheterization, and great care has been taken to change the fluid at frequent intervals. The possibility that the occlusion of the vessel might in some way be related to the pyrogenic reaction has been considered, but chills and fever have occurred in patients in which the catheter could not be put in the correct position for inflation. Perhaps the one constant relationship was that chills and fever were more likely to occur in those cases in which difficulty was encountered in placing the catheter and repeated manipulation of the catheter was necessary. As stated, however, this complication was never of serious proportions.

2. Ventricular extrasystoles occurred almost invariably during manipulation of the catheter as it passed through the right ventricle. Normal sinus rhythm immediately returned following withdrawal of the catheter into the right auricle. Once the catheter was in position in the pulmonary artery, extrasystoles did not occur. This complication was of no significance with the possible exception of one case in which auricular fibrillation ensued as the study was completed. Rapid digitalization was accomplished and two days later this patient underwent an uneventful pneumonectomy. The case is presented in detail.

CASE REPORT.—W. W., G.H.U.P. 217719, a 66-year-old man, was admitted to the hospital with hemoptysis of four months' duration. Roentgenograms of the chest revealed a mass lesion in the right hilar area. Bronchoscopy was performed and a positive Papanicolaou

was obtained. The vital capacity and maximum breathing capacity were within essentially normal limits. VC was 3,330 c.c. (calculated normal = 3,885) and MBC was 90 L. per minute (calculated normal = 109 L. per minute). Catheterization studies were carried out. The study went well and rapidly and was completed in about one and one-half hours. There were a few extrasystoles as the catheter passed through the right ventricle but nothing unusual. Immediately following withdrawal of the cardiac catheter, while the continuous electrocardiographic tracing was being made, it was noted that the patient suddenly began having auricular fibrillation. Immediate digitalization was carried out and he was rapidly controlled. Forty-eight hours later thoracotomy was performed. He was found to have a carcinoma of the lung and metastases were present in the mediastinal lymph nodes. A radical pneumonectomy and excision of the mediastinal nodes in the hilum and along the trachea were carried out. He withstood the operative procedure very well, and his postoperative course was entirely benign. He was discharged from the hospital without digitalis, on the tenth postoperative day.

3. A single major complication has occurred following the procedure. Although there is reasonable doubt as to whether it was a direct result of the procedure, it is nonetheless considered as a complication. The case is presented in detail.

CASE REPORT.—G.H.U.P. 224660. A 38-year-old man was admitted to the hospital with severe dyspnea and recurring bouts of cyanosis. The patient was well and carrying on his occupation of a garbage collector without any difficulty until four months prior to admission. At that time, while loading a truck, he suddenly became extremely short of breath, began to perspire profusely and had severe pain in the lower chest and upper abdomen. He was immediately taken to a hospital elsewhere where he was noted, also, to be cyanotic. He was placed in an oxygen tent and treated supportively with only minimal improvement. He was transferred to the Graduate Hospital of the University of Pennsylvania approximately ten days after onset of his illness. Examination at this time revealed an acutely ill man who became severely dyspneic and cyanotic on only slight exertion. Uncontrolled auricular fibrillation was present. There was cardiac enlargement and an apical systolic murmur, felt by the cardiologists to be consistent with a diagnosis of rheumatic heart disease with mitral insufficiency. Roentgenograms of the chest, in addition to revealing cardiac enlargement, showed obliteration of the right costophrenic sulcus due to a small effusion or a pleural thickening and a fine nodular infiltration throughout both lung fields. In view of the clinical history of breaking fluorescent lamps in the garbage, it was felt that the pulmonary changes were consistent with a diagnosis of berylliosis.

Since there was no history of rheumatic fever, and since chamber analysis of the heart revealed not only a left auricular enlargement but also an enlargement of all cardiac chambers, it was felt that the cardiac findings might also be on the basis of the pulmonary pathology or perhaps on the basis of some congenital defect. Studies performed were as follows: The PPD test was negative. The iodine uptake was normal. The timed vital capacity was 88 per cent of normal. Blood gas analyses from the femoral artery revealed a pCO_2 of 43, an arterial O_2 saturation of 83 per cent, and a pH 7.43. Intercostal pulmonary biopsy was carried out and revealed marked congestion. The specimen was analyzed for beryllium content and this was found to be significantly elevated. Routine cardiac catheterization was requested primarily to determine the presence of a possible congenital anomaly, but in view of the pulmonary findings it was felt that studies proximal and distal to an occluding balloon in the pulmonary artery might be revealing (Fig. 4).

Cardiac catheterization was carried out nine days after digitalization was instituted, although at the time of study the heart was still fibrillating. A No. 8 double lumen cardiac catheter was rapidly passed through an arm vein into the right pulmonary artery and a second No. 5 cardiac catheter was passed into the pulmonary conus in order to allow for recordings both proximal and distal to the occluding balloon. Studies were then made with

the balloon occluded (see below), and following completion of this, the routine pressures and blood samples were taken from the pulmonary artery, right ventricle, right auricle, and superior vena cava. There was no evidence of congenital anomaly either from the passage of the catheter, or from the results. Studies did, however, reveal a marked elevation of the pulmonary capillary pressures and elevation of both the pulmonary artery and right ventricular pressures.

Pulmonary capillary pressure	= 90/40 -	corrected mean 50
Pulmonary artery	= 80/10 -	corrected mean 28
Right ventricle	= 74/10 -	corrected mean 24
Right auricular	= 20/8 -	corrected mean 8
Superior vena cava	=	corrected mean 10

The findings were felt to be consistent with severe mitral stenosis.

The study took one hour and forty-five minutes and, although the patient perspired rather profusely during it, he tolerated it well. There was no appreciable elevation of the temperature immediately postcatheterization, and he was able to be up and about soon after returning to his bed. About twelve hours after catheterization, in the middle of the night, he fell out of bed and, on examination, was found to have a right-sided hemiplegia.

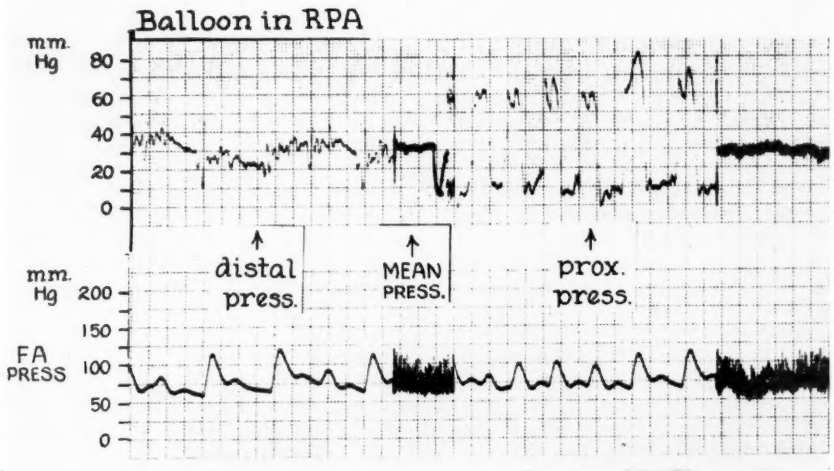


Fig. 4.—Catheterization studies on a 38-year-old man with berylliosis and severe mitral stenosis. The right pulmonary artery (RPA) was occluded by the balloon. The upper tracing is from the pulmonary artery, the lower from the femoral artery (FA). In this instance, proximal and distal pressures were made on the same channel. Note the change in the character of the tracing as recorded distal and proximal to the occluding balloon. Note that the mean pressures both proximal and distal are essentially the same.

He was seen by a neurological consultant who felt that he had had a cerebral vascular accident on the basis of an embolic or thrombotic episode involving a branch of the middle cerebral artery. He was placed on heparin and improvement gradually occurred. After approximately three months, good function returned to his right leg, but the upper extremity remained impaired.

While it is questionable whether or not the catheterization was related to the subsequent episode, we nonetheless feel that it should be considered as a complication. He perspired profusely during the procedure, and it is conceivable that hemoconcentration occurred with an increased thrombotic tendency. We feel the study was justified and, as a result of it, the diagnosis was established.

RESULTS AND DISCUSSIONS

Our investigations utilizing this method of study have been along two general lines: (1) study of lung function and pulmonary physiology, and (2) the study of pulmonary embolism, which is discussed in detail elsewhere.[10, 11]

A. *Pulmonary Artery Pressures.*—Occlusion of the right or left pulmonary artery was carried out in this group of patients for between twenty and sixty minutes, with an average occlusion time of forty minutes. No attempt was made to continue occlusion for longer than one hour. In some cases, occlusion would be carried out in a lobar artery for twenty minutes or more and then the balloon would be deflated, the catheter gently withdrawn into the main branch of the pulmonary artery, and the balloon again inflated for twenty to twenty-five minutes.

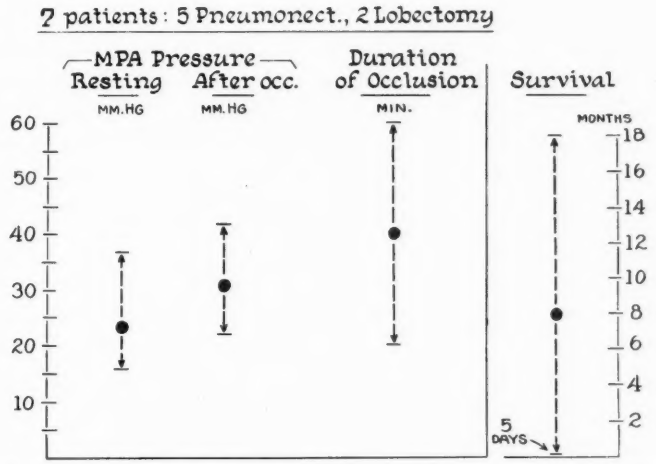


Fig. 5.—Results of pressure studies in 7 patients who had sustained increments in main pulmonary artery pressure following occlusion and who are now all dead following resectional therapy. The average value and the extremes are shown. The increment following occlusion in this group of patients averaged 8 mm. Hg.

The usual response to occlusion of the pulmonary artery to the right or left lung has been a transient increase of around 4 to 8 mm. Hg in the main pulmonary artery, and a return to pre-occlusion levels within ten to twenty minutes. The importance of a resting elevation of the main pulmonary artery pressure and a sustained increment following occlusion was emphasized by Carlens and his associates[1, 3] and in our earlier report.[2] The significance of these observations was recently further emphasized in the subsequent report by Bagger and his associates.[4] In reporting on 109 patients carefully studied and followed for three to four years, they found that, in their entire series, the mean resting pressure was between 18 and 19 mm. Hg which they considered to lie within the upper limits of normal values. They were able to divide their patients in-

to three groups, namely, those who died following resection, those who were invalids following resection, and those who were fit for work following resection. They found that the patients who died had a mean pressure of 22.2 mm. Hg, and felt that this reading was significantly higher than those readings in the invalid group and in that group of patients who had returned to work. Our results with respect to the pulmonary artery pressures are entirely in agreement with theirs. We have noted also that very small increments in pressure offered a grave prognosis. Since our patients were considerably older than those reported by these investigators, our mean control pressures were somewhat higher, but the sustained increment following occlusion was of a similar order. The average mean control resting pressure in our series of patients was 23.5 mm. Hg, and the average increment in the patients having sustained elevation was 8 mm. Hg (5, 8, 16, 8, 6, and 4 mm. Hg).

Thirty-two of the 35 patients whom we studied were subsequently operated upon. Resectional therapy was carried out upon 20 patients. Of this group of twenty, 7 had elevated pulmonary artery pressures on their catheterization studies and all are now dead (Fig. 5). Five of these patients had pneumonectomies and the average length of survival following operation was 6.1 months (five days, nine days, six months, one year, and one year). Two of the patients had lobectomies, with an average length of survival following operation of thirteen months (eight months and eighteen months). All of these patients were severely dyspneic during the postoperative period. The dyspnea was much more marked following operation than prior to the resectional therapy. It would appear from our own studies and from those of others[3, 4] that the fundamental factor is the sustained increment in pressure following occlusion rather than a resting elevation, since 2 out of these 7 patients had normal resting pressures but a sustained elevation following occlusion.

CASE REPORT.—C. S., G.H.U.P. 223462, a 56-year-old man was admitted to the hospital with a chief complaint of severe coughing spells and shortness of breath of approximately seven years' duration. In 1946, drainage of an empyema was carried out and he did well for several years after that except that he continued to cough and continued to have large amounts of sputum. The sputum production had gradually increased to around a pint a day and was very foul smelling, greenish, and purulent. Roentgen examination of the chest revealed multiple radiolucencies associated with fluid levels in the right lower lobe due to cystic bronchiectasis. There were many linear opacities and round radiolucencies in the right upper lung field, evidently due to an old chronic inflammatory process. Bronchography revealed a severe cystic bronchiectasis of the entire right lung. Arterial blood gas analyses revealed a pH of 7.43, oxygen content of 17.2 volumes per cent, CO_2 content of 51.5 volumes per cent and oxygen saturation of 93 per cent. The vital capacity was 62 per cent of normal and the maximum breathing capacity was 48 per cent of normal with an actual measurement of 47.9 L. and an estimate of 100.2 L. Catheterization studies with balloon occlusion were carried out on this patient not only to obtain the usual studies, but also to attempt to determine if alterations in the oxygen saturation would occur following exercise, and occlusion and exercise. Exercise was performed on the treadmill for one minute. The results of the study are shown on the following table.

	O_2 SATURATION $\frac{A}{V}$ (%)	pCO_2 $\frac{A}{V}$ (MM.)	pH $\frac{A}{V}$
Control	92/72	42/47	7.40/7.38
After one-minute exercise	93/43	45/43	7.39/7.38
Ten minutes after occlusion	94/83	42/43	7.42/7.37
After one-minute exercise	90/54	42/46	7.40/7.39

Catheterization studies revealed a main pulmonary artery pressure of 16 mm. Hg with a sustained increment to 22 mm. Hg upon occlusion for thirty minutes. Although we realized that the ventilatory function studies were poor, we felt that the pressure increase was not sufficiently great to contraindicate surgery. An uneventful pneumonectomy was performed. Despite evidence of good aeration of the remaining lung, the patient had severe dyspnea and cyanosis on the slightest exertion during the postoperative period. On the ninth postoperative day following a bout of coughing, he became extremely dyspneic and suddenly died. At necropsy, except for moderate atelectasis of the basilar segments of the left lower lobe, no other abnormalities were found.

This patient with severe cystic bronchiectasis involving the entire right lung had poor ventilatory studies. The catheterization studies revealed a resting pressure of 16 mm. Hg and, following occlusion for thirty minutes, it rose to 22 mm. Hg. At this time we did not appreciate the significance of this small variation[4] and we felt that, on the basis of the catheterization studies, he could withstand pulmonary resection. A pneumonectomy was therefore carried out. The patient was severely dyspneic and cyanotic on the slightest exertion during the postoperative period and died on the ninth postoperative day following a bout of coughing. In the face of the detailed studies previously mentioned,[4] the significance of the small increment which this patient had, following occlusion, becomes apparent.

B. *Blood Gases.*—Study of the blood gases thus far has not been very productive. Following occlusion of the bronchus, the arterial oxygen saturation has fallen, although it has returned to control levels following the administration of 100 per cent oxygen for five minutes. Whether this fall is indicative of poor pulmonary function, or whether it is due to some degree of stenotic breathing incident to the methods used has not been entirely determined, but is now being studied. It should be pointed out that while we felt some degree of stenotic breathing did occur with the Carlens-Stille endotracheal catheter, this is not in any way meant to detract from this very excellent catheter which has proved so successful clinically. Undoubtedly, we were subjecting it to a very severe test by the methods used, and it would be much more reasonable to place a cardiac catheter with a balloon on the tip of it into the respective bronchus and to occlude it in this manner rather than with the endotracheal tube in the unanesthetized patient.

C. *Study of the Pressures and Blood Gases Distal to the Occluding Balloon.*—With the use of the triple lumen catheter we have studied these values routinely in the more recent patients. In control studies, it was found that the pulmonary artery pressure immediately distal to the occluding balloon, whether the balloon was in the main branch of the pulmonary artery or one of the lobar arteries, fell to an average value of 10 mm. Hg, the normal pulmonary capillary pressure, and the contour of the tracings changed to a pulmonary capillary-type tracing or a wedge-type tracing (Fig. 6). Presumably, distal to the occlusion, there is a common chamber consisting of left atrium, pulmonary veins, pulmonary

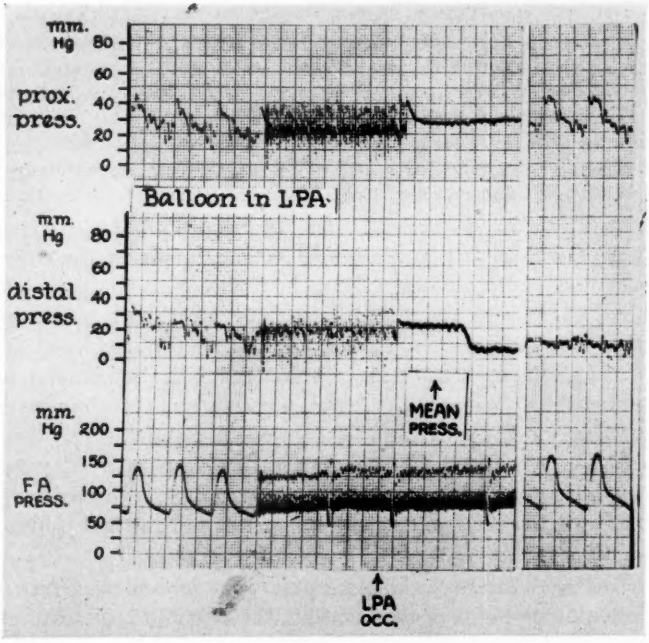


Fig. 6.—Results of catheterization studies in a 73-year-old man with a carcinoma of the lung. The catheter was placed in the left pulmonary artery (LPA). Note the fall in pressure distal to the balloon, following complete occlusion. The pressure fell to 8 mm. Hg mean and the tracing changed to a wedge-type contour. Following occlusion, the proximal pulmonary artery pressure rose from 26 mm. Hg mean to 32 mm. Hg mean but returned to control levels within ten minutes. This patient had a nonresectable lesion.

capillaries, and the occluded pulmonary artery segment. Brofman[6] has applied the term "lacunar" to this more or less quiet lake. In both Brofman's studies and our own, the distal pressure has been proved to be as reliable as the wedge pressure. The importance of these findings may be illustrated by 2 cases.

CASE REPORT.—G.H.U.P. 224660 (see above). In the patient with berylliosis and mitral stenosis who was having severe bouts of dyspnea and cyanosis, despite complete occlusion of the right pulmonary artery as attested by alteration of the contour of the distal tracing as

compared to the proximal tracing, the distal pressure remained markedly elevated at around 30 mm. Hg (mean pressure) (Fig. 7). Elevation of the "pulmonary capillary" pressure in the face of the severe mitral stenosis which this patient had would have been anticipated.

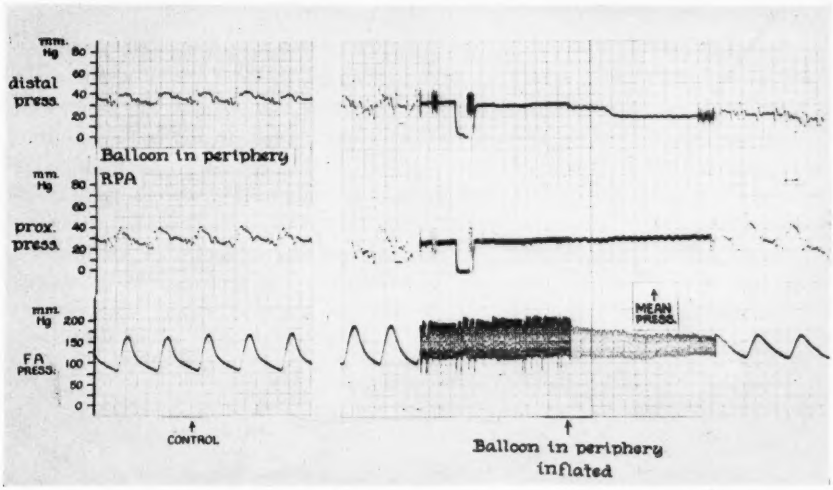


Fig. 7.—Results of catheterization studies in a 56-year-old man with carcinoma of the lung and aortic stenosis. The balloon was placed in a lobar artery of the right lung. Periphery as used in the tracing refers to the lobar artery as opposed to the main branch of the pulmonary artery. Note that the control proximal and distal pressures are essentially the same and the contour of the tracing is similar.

Following the occlusion of the lobar artery, the distal pressure fell but not to the levels that would ordinarily have been obtained (see Fig. 6); i.e., the fall was from 32 to 20 mm. Hg mean but still considerably above the average normal mean pulmonary capillary pressure. Note the change in the contour of the distal tracing following occlusion of the vessel.

CASE REPORT.—J. R., G.H.U.P. 224731, a 56-year-old man, was admitted to the hospital with hemoptysis of approximately three months' duration and a more recent bout of massive bleeding from the gastrointestinal tract. Intensive gastrointestinal study was essentially negative but roentgenogram of the chest revealed a lesion of the right lung. Bronchoscopic biopsy was carried out and was positive for carcinoma. The patient was also known to have aortic stenosis. Catheterization studies were carried out with particular reference to the pressures and blood gases both proximal and distal to the occluding balloon. The mean proximal resting pressure was 22 mm. Hg and rose to 26 mm. Hg after twenty minutes of occlusion. The distal pressure, although falling slightly, remained abnormally elevated after occlusion of the balloon; namely, in the range of 18 mm. Hg mean pressure despite complete occlusion.

Although it was known that the patient had aortic stenosis and, since the routine pulmonary function studies were not particularly remarkable and the pulmonary artery pressure was not appreciably elevated, it was decided to proceed with surgery. A right pneumonectomy was carried out without difficulty. On the fourth day following operation, the patient suddenly developed acute left heart failure which failed to respond to intensive therapy and died. Necropsy revealed an extremely severe aortic valvular and subvalvular calcific stenosis and pulmonary edema. Since the distal recording actually represented

the pulmonary capillary pressure, and since the pulmonary capillary pressure is generally held to be essentially the same as the pulmonary vein and left auricular pressure, then it becomes apparent that, even at rest preoperatively, this patient was having some degree of left heart strain.

Blood gas analyses distal to the occluding balloon in a lobar artery have revealed blood completely saturated with oxygen (Fig. 8). Actually, the distal sample invariably has had a higher oxygen content than the brachial artery and the pulmonary capillary sample. That this complete saturation is due to a long equilibration time between ventilated alveoli and stagnant capillary blood is indicated not only by the fact that the oxygen saturation exceeds that in the systemic circulation but also by the very low pCO_2. As Brofman states,[6, 7] presumably distal to occlusion retrograde flow and oxygenation of blood is

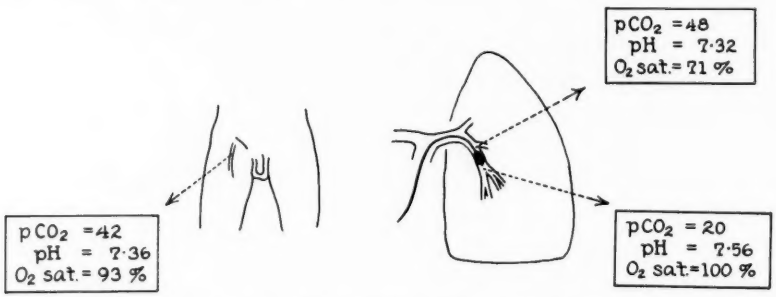


Fig. 8.—Analysis of the blood gases both proximal and distal to the occluding balloon which in this instance was placed in a lobar artery. The distal sample was taken five minutes after occlusion. Note that the oxygen saturation exceeds that in the femoral artery.

taking place very rapidly. We feel that these studies supply further evidence that no precapillary anastomosis exists between the pulmonary and bronchial circulations and would appear to refute observations that bronchial artery flow, following pulmonary artery occlusion, increases as a result of a fall in pulmonary capillary pressure.

SUMMARY AND CONCLUSIONS

Unilateral pulmonary artery occlusion has now been carried out in almost 300 patients by various groups employing this method of study without mortality, nor any serious sequelae other than that reported by us. While it is a difficult and arduous study, and certainly not applicable for use as a routine method of investigation, it has proved to be very valuable in those borderline cases, particularly in patients with tuberculosis, where there is some question whether the patient's resection tolerance will be exceeded. While in our own studies we have been reluctant to withhold operation on the basis of positive findings in the study, it now seems clear from the collected experience that this would be justified and is even indicated, particularly in those patients not having malignant disease. Even in those having malignant disease, when the findings have been positive, an operation has had little to offer. In this latter

situation such studies as these would, however, indicate the importance of doing a lobectomy rather than a pneumonectomy in carcinoma, provided it is feasible, when there is evidence that the resection tolerance of the patient would not be able to stand a pneumonectomy. The particular finding which has been universally obtained and which has indicated unequivocally a poor prognosis has been that of an elevation of the resting pulmonary artery pressure with a sustained increment following occlusion. Even if the resting pressure is not elevated, a sustained increment following occlusion has shown a poor prognosis.

A study of the pressures and the gas analyses distal to the occluding balloon has also yielded positive information with regard to the patient's ability to withstand pulmonary resection. In addition, this type of study has also indicated that there are no precapillary anastomoses between the pulmonary and systemic circulations. We feel that this method of study has great possibilities in the study of lung function, pulmonary vascular anatomy, and pulmonary embolism. The latter phase of this problem is under investigation by us and is being reported in detail elsewhere.

REFERENCES

1. Carlens, E., Hanson, H. E., and Nordenström, B.: Temporary Unilateral Occlusion of the Pulmonary Artery, J. THORACIC SURG. **22**: 527, 1951.
2. Nemir, P., Jr., Stone, H. H., Mackrell, T. N., and Hawthorne, H. R.: Controlled Unilateral Bronchovascular Occlusion as a Method for Studying Pulmonary Function: A Preliminary Report, Surgery **34**: 401, 1953.
3. Hanson, H. E.: Temporary Unilateral Occlusion of the Pulmonary Artery in Man: A Method for Preoperative Determination of the Function of Each Lung, Acta chir. scandinav., Supplement 187, Stockholm, 1954.
4. Bagger, M., Carlens, E., Hanson, H. E., Malmstrom, G., Uggla, L. G.: Indications for and Results of Thoracic Surgery With Regard to Respiratory and Circulatory Function Tests. To be published.
5. Sloan, H., Morris, J. D., Figley, M., Lee, R.: Temporary Unilateral Occlusion of the Pulmonary Artery in the Preoperative Evaluation of Thoracic Patients, A Preliminary Report, J. THORACIC SURG. **30**: 591, 1956.
6. Brofman, B. L.: Unilateral Pulmonary Artery Occlusion for Studying Lung Function and Pulmonary Hemodynamics. To be published.
7. Brofman, B. L.: Personal communication.
8. Carlens, H. E.: Personal communication.
9. Sloan, H.: Personal communication.
10. Nemir, P., Jr., Stone, H. H., Mackrell, T. N., Hawthorne, H. R., Studies on Pulmonary Embolism Utilizing the Method of Controlled Unilateral Pulmonary Artery Occlusion, Philadelphia, 1955, Proc. Surg. Forum, Am. Coll. Surgeons, W. B. Saunders Company, p. 210.
11. Stone, H. H., and Nemir, P., Jr.: Studies on Pulmonary Embolism—Effect of Histamine and 5-Hydroxy Tryptamine Injected Distal to Occluding Balloon in Pulmonary Artery. To be published.

OXYGEN AVAILABILITY TO THE BRAIN DURING INFLOW OCCLUSION OF THE HEART IN NORMOTHERMIA AND HYPOTHERMIA

SAMUEL KAPLAN, M.D. (BY INVITATION), EDWARD C. MATTHEWS, M.D.* (BY INVITATION), LOUIS SCHWAB, M.D. (BY INVITATION), AND LELAND C. CLARK, JR., PH.D. (BY INVITATION)
CINCINNATI AND YELLOW SPRINGS, OHIO

MANY of the surgical techniques used in the therapy of intracardiac anomalies under direct vision depend on the application of either one or the other of two principles. These are: (a) the low flow rate or azygos principle based on the fact that the function of vital organs can be temporarily maintained on a cardiac output much reduced from normal,[1] and (b) the reduction of metabolism induced by hypothermia which lowers the oxygen requirements of the body thus permitting temporary occlusion of the circulation.[2] The application of either of these methods necessarily reduces the oxygen availability to vital organs. The purpose of this study is to determine the degree of change in oxygen availability to the brain during low flow rates and during hypothermia with temporary interruption of the circulation.

METHOD

The oxygen availability to the brain was measured by the polarographic technique which depends on the reduction of oxygen at a suitable cathode. If this cathode is maintained at about –0.6 volts with respect to a nonpolarizable anode, the current which flows, as oxygen is reduced, is proportional to the oxygen content of the tissue. Mongrel dogs weighing between 9 and 18 Kg. were prepared by the insertion of a platinum or gold cathode into the parietal lobe of the brain. The platinum electrodes consisted of 26-gauge platinum wire insulated in glass and having a 3 mm. exposed tip.[3] Gold cathodes were constructed from 26-gauge nylon insulated copper wire with an exposed tip of 5 mm. which was silver plated and then gold plated. These cathodes were left in situ for five to fifteen days before the experimental procedures to be described below were carried out. A silver chloride reference electrode placed subcutaneously was used as the anode. A variable shunt was used to compensate for variations in current flow from the cathode. The current flow resulting from the reduction of oxygen was continuously recorded with a direct writing suspension type photoelectric galvanometer.

From the Children's Hospital Research Foundation and the Department of Pediatrics, College of Medicine, University of Cincinnati, Cincinnati, Ohio and from the Fels Institute for Research in Human Development, Antioch College, Yellow Springs, Ohio.

This project was supported in part by grants from the United States Public Health Service (705-C) and the Cincinnati Children's Heart Association.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7-9, 1956.

*This work was done during the tenure of a Research Fellowship of the American Heart Association.

The animals were anesthetized with intravenous sodium pentobarbital (25 mg. per Kg.). The gas mixtures, described later, were given through a closed endotracheal system. Continuous records of brain oxygen availability were started soon after the induction of anesthesia and continued for the duration of the experiment. A thoracotomy was performed through the right fourth intercostal space and the superior and inferior venae cavae and the azygos vein were isolated. Temperatures were recorded from the rectum, right auricle, and brain. A thermistor[4] with a long lead was threaded through the femoral vein to the right auricle. Brain temperatures were obtained by inserting a thermistor mounted in a 20-gauge needle into the brain on the contralateral side to that of the cathode. The effects of low flow rate on the brain oxygen availability were then tested by occlusion of the inferior vena cava and superior vena cava cephalad to the azygos vein while the animal was being ventilated with 100 per cent oxygen. After a suitable recovery period, with total circulation intact, the animals were manually ventilated in sequence with 21, 10.27, and 4.91 per cent oxygen in nitrogen allowing a return of the brain polarographic record to a stable base line following the administration of each gas mixture. The carbon dioxide content of the above gas mixtures was less than 0.04 per cent.

A hypothermic state was then induced by extracorporeal cooling using the pump described by Clark and his associates.[5] The pump was filled with compatible donor blood containing 20 to 25 mg. heparin* per liter. The subject was given 1.0 mg. heparin per Kg. prior to extracorporeal circulation. Blood was obtained from one femoral artery and circulated through a stainless steel coil immersed in ice water. The cooled blood was returned to the arch of the aorta through a catheter inserted into the other femoral artery. By this method the brain temperature was reduced to about 28° C. in eleven to twenty-three minutes. The rate and degree of fall of temperature in the three sites measured was closely parallel. In the hypothermic state, oxygen availability to the brain was measured during complete circulatory occlusion and during the administration of the gas mixtures described above with an intact circulation. All animals were sacrificed after termination of the experiment.

RESULTS

The results of the above experimental procedures are presented graphically in Figs. 1-4. Oxygen availability to the cathode which reflects brain oxygen availability is expressed as a percentage change from control levels. In all the graphs the heavy interrupted line indicates the mean change in oxygen availability and the shaded area represents the range of variation. Fig. 1 shows the change in oxygen availability to the brain during low flow rates in normothermia in which the superior and inferior venae cavae were occluded temporarily with the azygos vein intact. It represents eight experiments carried out in 5 dogs. Within fifteen seconds after venous occlusion oxygen availability begins to change and is reduced to about 55 per cent of the control level at the end of one minute. Thereafter there is a more gradual fall to a relatively steady base line which represents a mean reduction of about 70 per cent in

*The heparin in this project was kindly supplied by The Upjohn Co., Kalamazoo, Mich.

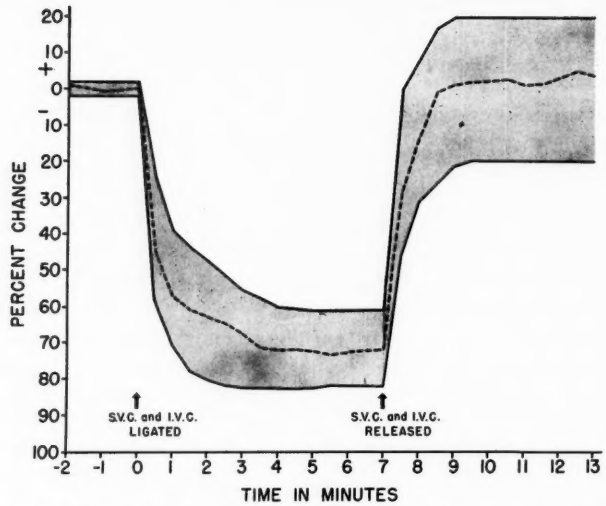


Fig. 1.—Per cent of change in oxygen availability to the brain in normothermia (azygos principle) during occlusion of the inferior and superior venae cavae with the azygos vein intact.

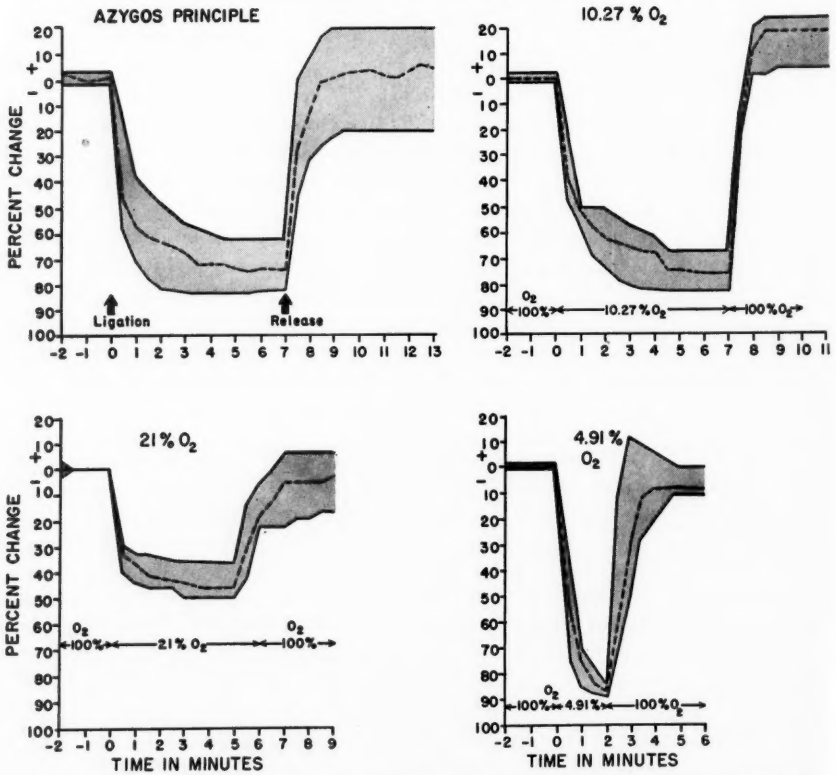


Fig. 2.—Comparison of changes in oxygen availability to the brain in normothermia during azygos flow and during ventilation with 21, 10.27, and 4.91 per cent oxygen in nitrogen.

oxygen availability. This level is reached in about four minutes. When normal venous return to the heart is re-established the events following venous occlusion are reversed with an abrupt and rapid rise followed by a slower gradual rise toward the control levels.

In an attempt to obtain an in vivo calibration of brain oxygen availability the normothermic animals were ventilated with gas mixtures containing varying amounts of oxygen. Fig. 2 indictates the percentage change in oxygen availability to the brain during the ventilation with gas mixtures containing 21, 10.27, and 4.91 per cent oxygen with an intact circulation. The similarity

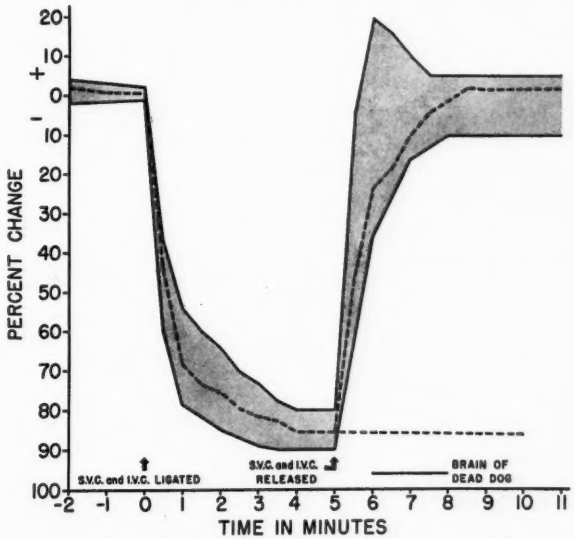


Fig. 3.—Per cent of change in oxygen availability to the brain in hypothermia during complete circulatory occlusion. Brain temperature, 26.5° to 29.5° C.

between the curves resulting from the breathing of 10.27 per cent oxygen and that resulting from low flow (azygos flow) is apparent. In both instances there is an immediate and rapid reduction in oxygen availability which stabilizes to a mean value of 70 per cent or less of the control reading within a period of about four minutes. The return toward control levels is immediate when the animals are allowed to breathe 100 per cent oxygen with the circulation intact.

Fig. 3 shows the change in oxygen availability to the brain in hypothermia with complete inflow venous occlusion. This graph represents nine experiments in 5 dogs in which the brain temperature varied from 26.5° to 29.5° C. Immediately after total inflow occlusion there is a rapid fall in brain oxygen availability with a mean decrease of 86 per cent from the control level after a period of about four minutes. Occlusion of the aorta and pulmonary artery during venous occlusion did not significantly alter the reading. Stability of the reading, after the fall of oxygen availability is complete, is indicated by the continuation of the mean curve (Fig. 3) in which, in one instance, inflow

occlusion was maintained for a period of ten minutes. Coincidentally, this reading fell on the mean. The return of oxygen availability toward control levels is rapid after restoration of the normal circulation. It is noteworthy that the reading obtained during hypothermia with circulatory occlusion is only 10 per cent higher than the base line obtained from the brain of the dead hypothermic animal (Fig. 3).

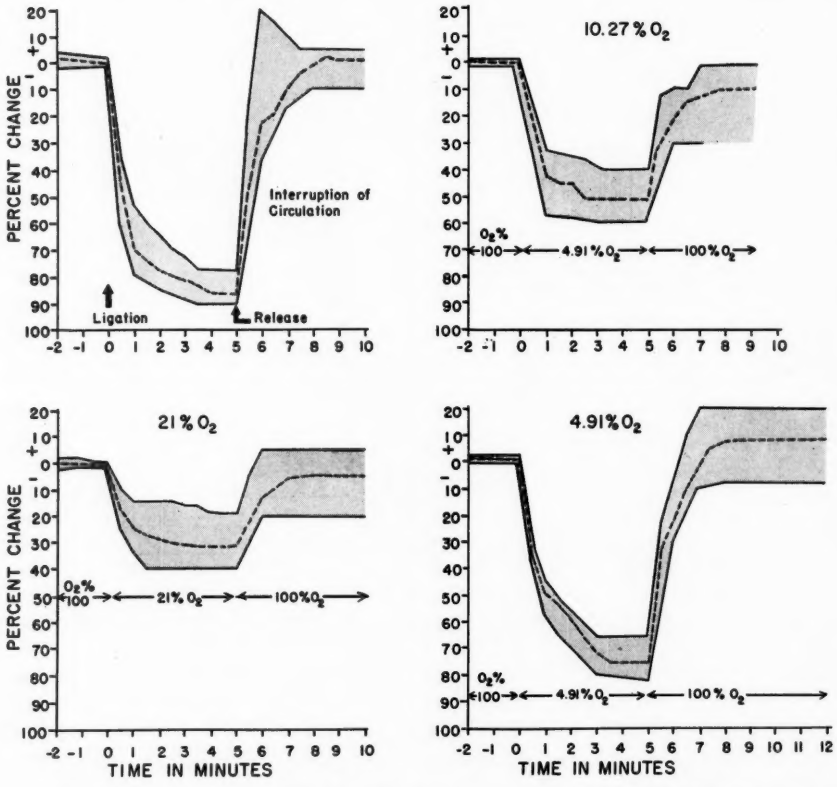


Fig. 4.—Comparison of changes in oxygen availability to the brain in hypothermia during complete circulatory occlusion and during ventilation with 21, 10.27, and 4.91 per cent oxygen in nitrogen. Brain temperature, 26.5° to 29.5° C.

Fig. 4 shows the change in oxygen availability to the brain in hypothermia during ventilation with 21, 10.27, and 4.91 per cent oxygen in nitrogen as compared with the reading obtained during circulatory occlusion in hypothermia. It is notable that the reading obtained during circulatory occlusion is somewhat lower than that obtained during the ventilation with 4.91 per cent oxygen. In both instances there is an immediate and rapid reduction of oxygen availability. The return toward control levels is immediate when the animals are allowed to breathe 100 per cent oxygen with the circulation intact.

DISCUSSION

The electrical output of the polarographic cathode is a function of the oxygen available in the immediate environment of its active tip. Thus, this cathode will measure oxygen brought to it both by free diffusion of the gas and by mechanical fluid transport. With such a cathode situated in the brain, availability of oxygen to the cathode reflects local brain oxygen availability.

The change in oxygen availability to the brain during temporary occlusion of the inferior vena cava and superior vena cava cephalad to the azygos have been described (see Fig. 1). It is noted that although there is uniformly an abrupt fall in oxygen availability to the brain after venous occlusion, the degree of fall and the return to control levels is variable. This variation could be explained on individual differences in the depth of anesthesia and the degree of reduction of the cardiac output. During occlusion of the inferior vena cava and superior vena cava cephalad to the azygos, the cardiac output depends primarily on the venous return through the azygos vein and the coronary venous system. Because these two fractions are variable, the cardiac output, although markedly reduced in all instances, is also variable.

Although the oxygen availability to the brain during low flow rates (azygos flow) and during ventilation with 10.27 per cent oxygen in normothermia are similar, it is appreciated that the dynamics of cerebral circulation are not comparable during the above two circumstances. In the former the brain is perfused with a low blood flow containing a high tension of oxygen, whereas in the latter, it is perfused with a high blood flow[6] at low oxygen tensions. Despite this variability in cerebral hemodynamics in the above two circumstances, these experiments indicate that the oxygen availability to the brain is nevertheless comparable.

A comparison of the changes in oxygen availability to the brain during the breathing of various gas mixtures in normothermia and hypothermia is of interest. In general, there was a larger and more rapid decrease in oxygen availability during the breathing of the same gas mixture in normothermia as compared to hypothermia. Also during the breathing of 4.91 per cent oxygen in normothermia, hyperventilation occurred after a period of about two minutes which necessitated the reinstitution of ventilation with 100 per cent oxygen. In hypothermia, the animals were ventilated for three to five minutes with 4.91 per cent oxygen without the appearance of hyperventilation. This clinical sign is interpreted to be the result of hypoxia. Since these experiments indicate that there is a marked reduction in brain oxygen availability in the hypothermic dog breathing 4.91 per cent oxygen although the clinical signs of hypoxia are not apparent, the possibility is raised that hypothermia may mask the signs of hypoxia.

It is noted in Fig. 3 that a small current flow is still detectable in the brain of the dead hypothermic animal. This may be due to minute amounts of polarographically active material, for example, iron or redox active substances.

In vitro experiments have shown that the current flow from a bare platinum cathode exposed to the same tension of oxygen in saline solution may be increased fivefold or more if the saline solution is agitated (stirring effect). It

is not known whether this effect occurs during the measurement of tissue oxygen availability. Experiments are in progress to compare the oxygen availability in the brain with cathodes described above and with cathodes unaffected by stirring with which quantitative determinations of tissue oxygen tension may be made. If a stirring effect occurs in tissues, one of the factors which would influence it would be the movement of blood and interstitial fluid in the environment of the cathode. A reduction of cerebral blood flow may conceivably result in an abrupt drop of oxygen availability while tissue oxygen tension falls at a slower rate. The relative importance in cerebral metabolism of brain oxygen availability as oppossed to brain oxygen tension warrants further investigation.

It is appreciated that brilliant results have been obtained by the use of low perfusion rates or hypothermia during the surgical therapy of intracardiac anomalies under direct vision. These experiments indicate that in either circumstance, oxygen availability to the brain is significantly reduced. It is possible that the protection afforded to the brain by hypothermia may not depend only on a decreased oxygen need. Furthermore, the reduction in oxygen availability in association with extremely low flow rates (azygos flow) may approach levels only slightly in excess of those resulting in brain hypoxia.

SUMMARY

A. Oxygen availability to the brain of dogs was measured polarographically during the following conditions: (a) temporary occlusion of the inferior vena cava and superior vena cava cephalad to the azygos vein (azygos principle), and (b) circulatory occlusion in hypothermia.

B. In normothermia, the oxygen availability to the brain drops precipitously after occlusion of the inferior and superior venae cavae with the azygos vein intact. It reaches an average level of 70 per cent below the control in a period of about three minutes.

C. The oxygen availability curve described in B is most closely reproduced by the breathing of 10.27 per cent oxygen.

D. In hypothermia with complete circulatory occlusion, the oxygen availability to the brain falls rapidly and precipitously to an average level of 86 per cent below the control.

E. The oxygen availability curve described in D is most closely reproduced by the breathing of less than 4.91 per cent oxygen.

REFERENCES

1. Cohen, M., and Lillehei, C. W.: A Quantitative Study of the "Azygos Factor" During Vena Caval Occlusion in the Dog, Surg., Gynec. & Obst. **98**: 225, 1954.
2. Swan, H., Virtue, R. W., Blount, S. G., and Kircher, L. T.: Hypothermia in Surgery, Analysis of 100 Clinical Cases, Ann. Surg. **142**: 382, 1955.
3. Clark, L. C., Wolf, R., Granger, D., and Taylor, Z.: Continuous Recordings of Blood Oxygen Tensions by Polarography, J. Appl. Physiol. **6**: 189, 1953.
4. Clark, L. C., and Trolander, H., Thermometer for Measuring Body Temperature in Hypothermia, J. A. M. A. **155**: 251, 1954.
5. Clark, L. C., Hooven, F., and Gollan, F.: A Large Capacity, All-Glass Dispersion Oxygenator and Pump, Rev. Sci. Instrum. **23**: 748, 1952.
6. Kety, S. S., and Schmidt, C. F.: The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, J. Clin. Invest. **27**: 484, 1948.

THE EFFECT OF SOMATOTROPHIN ON VENTRICULAR FIBRILLATION OF ARTERIOCLUSIVE AND HYPOTHERMIC ORIGIN

DAVID H. WATKINS, M.D., PH.D.* (BY INVITATION), ARTHUR E. PREVEDEL, M.D.* (BY INVITATION), GORDON A. MUNRO, M.D.* (BY INVITATION), S. ROTHMAN, PH.D.** (BY INVITATION), AND ROBERT M. HILL, PH.D.*** (BY INVITATION)
DENVER, COLO., AND LOS ANGELES, CALIF.

VENTRICULAR fibrillation belongs to the most serious accidents which occur in the course of anesthesia or operation. If untreated and if irreversible, it leads shortly to death.

Bovine somatotrophin† was administered to a series of dogs prior to the attempted induction of ventricular fibrillation by right ventriculotomy under hypothermic conditions or by one-stage coronary artery ligation in normothermic animals. Under control conditions such hearts fibrillate readily. However, those animals which had been premedicated were remarkably resistant to fibrillogenic stimuli. This experience leads us to believe that the mechanisms producing fibrillation may be modified on a metabolic level. The early local metabolic derangements produced by myocardial infarction are of special interest because of the production of ventricular fibrillation.

Bigelow[1] and his co-workers showed that the metabolic rate of dogs cooled to 20° C. (rectal temperature) is about 15 per cent of metabolic rate of control animals. Further studies by Bigelow[2] demonstrated that venous inflow occlusion could be undertaken for periods up to 15 minutes without demonstrable damage to the heart or central nervous system in those animals which survived the procedure; however, about one half of his animals died of ventricular fibrillation during the experiment.

Since that time an enormous number of experiments with intracardiac operations under hypothermia have been performed. During the past few years a growing number of operations on human subjects have also been carried out.

Senning[3] suggested that ventricular fibrillation might be used as an ideal state in which to operate at normal body temperature in connection with extracorporeal circulation. If the blood supply to the heart remains adequate, ventricular fibrillation is usually easy to reverse, both as regards experimental operations on animals and operations on man (Senning,[4] Helmsworth and his associates,[5] Glenn and Sewell[6]). Ventricular fibrillation has also been said to be equally useful with extracorporeal circulation as well as combined with hypo-

This project was supported by a grant from the Ruth and Vernon Taylor Foundation and by a grant from the Riker Laboratories.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

*Department of Surgery, University of Colorado School of Medicine, Denver, Colo.

**Research Division, Riker Laboratories, Los Angeles, Calif.

***Department of Biochemistry, University of Colorado School of Medicine, Denver, Colo.

†Supplied as "Riker 525" by the Riker Laboratories.

thermia (Juvenelle and co-workers,[7] Senning[8]). Ventricular fibrillation has also been recommended to facilitate intracardiac operations during hypothermia without combination with extracorporeal circulation; in this case, air embolism occurring in connection with the closure of the heart and resumption of the circulation is said to be prevented.

However, most surgeons have considered it advisable to avoid ventricular fibrillation if possible, without courting the hazards of electrical or chemical defibrillation. In studies regarding ventricular fibrillation, methods have been investigated to avoid this complication, and from them more definitive ideas regarding the nature, causes, and metabolic consequences have been discovered.

Montgomery and his co-workers,[9] while recognizing that it is currently impossible to characterize ventricular fibrillation at the cellular level, pointed to the increasing body of knowledge strongly implicating potassium maldistribution.

Not only is the occurrence of ventricular fibrillation in the hypothermic myocardium of direct practical concern to the surgeon, but the occurrence of fibrillation in ischemic myocardium from any cause is becoming of increasing surgical significance. Here again, potassium which is liberated from such ischemic muscle is the factor upon which definite evidence from a variety of experiments converge in unequivocal manner. If potassium is injected into a coronary artery of a dog with continuing circulation, it produces ectopic activity. Ischemic ventricular myocardium releases potassium in quantities sufficient to elevate the potassium concentration in the coronary venous blood from the ischemic area. Positive correlations can be demonstrated to exist between the periods of major elevation of potassium concentration in the muscle samples, and the periods of most intense ectopic ventricular activity. The potassium concentration in these samples decreases to approach the control levels at times which correspond approximately to the times when ectopic activity in the infarcted area disappears. The potassium content of infarcted muscle is greatly reduced at those times. Thus the evidence is overwhelming that locally liberated potassium is an excitatory agent for the remaining healthy myocardium (Harris[10]).

METHODS

Two groups of experiments are presented: those concerned with the effect of somatotrophin on ventricular fibrillation in hypothermia, and those concerned with the effect of somatotrophin on the fibrillation occurring consequent to ligation of a coronary artery.

The first group of experiments were carried out as follows. Mongrel dogs were placed in an ice-water bath after being deeply anesthetized with intravenous sodium pentobarbital (30 mg. per Kg.) to prevent shivering. Following tracheal intubation, the dog was hyperventilated with pure oxygen. When 29° C. rectal temperature was obtained, the dog was removed from the bath; a further drop of 3° to 6° C. of temperature occurred. Using aseptic technique, a right anterolateral thoracotomy incision was made through the fifth intercostal space. After entering the right thorax the azygos vein was ligated, pericardial sac opened widely, and both venae cavae were occluded.

In an initial series of experiments, the ascending aorta was occluded with a nonerushing clamp about 2.5 cm. distal to the coronary ostia. A control series of dogs received injections of saline solution. The experimental group was treated as follows. One hundred Choay units of somatotrophin (one Choay unit equals 0.2-0.5 Evans units) was administered by coronary perfusion. In an initial group of 5 dogs, no effect upon the onset of ventricular fibrillation could be demonstrated following right ventriculotomy.

In a second group of 5 experimental dogs, 100 units of somatotrophin were given intravenously immediately before occlusion of the venae cavae was carried out. This substance had no effect on the prevention of fibrillation following right ventriculotomy in this group.

The third experimental group received 100 units of somatotrophin 12 hours preoperatively and 100 units 4 hours preoperatively by intramuscular injections. Control animals received injections of saline solution. Following the institution of inflow stasis a 5 to 8 cm. incision was made in the right ventricle. After filling the heart with saline solution to prevent air embolism, the ventricular wall was sutured. The total occlusion time varied from 5 to 15 minutes, the average being 10 minutes.

Results: Right ventriculotomy is a fibrillogenic stimulus in the cold dog. Of 23 control dogs, all incurred fibrillation during ventriculotomy; many of these animals developed fibrillation with the initial stimulus. In those dogs to which somatotrophin was administered by coronary perfusion or to which it

TABLE I. SUMMARY OF DATA: HYPOTHERMIC DOGS RIGHT VENTRICULOTOMY AS A FIBRILLATORY STIMULUS

	NUMBER DOGS	VENTRICULAR FIBRILLATION	RESUSCITATION
Control	23	23	0 of 23 attempts
Somatotrophin, 100 units I. V. 5 minutes prior to inflow occlusion	5	5	0 of 5 attempts
Somatotrophin, 100 units by coronary perfusion immediately following inflow occlusion	5	5	0 of 5 attempts
Premedication with somatotrophin, 100 units 12 hours and 4 hours, preoperatively	32	11	6 of 11 attempts

was given intravenously 5 minutes before the institution of vena caval occlusion, no protective effect against ventricular fibrillation was noted. Among the 32 dogs which had been premedicated with somatotrophin, 100 units given 12 hours and 4 hours preoperatively by intramuscular injection, 11 developed ventricular fibrillation. In 6 of the 11, attempts at defibrillation and resuscitation by electrical shock were successful.

Similar experiments were carried out in experimental and control animals following ligations of coronary arteries.

Method.—Mongrel dogs were deeply anesthetized with intravenous sodium pentobarbital (30 mg. per Kg.). Following tracheal intubation, the dog was ventilated using the Phipps-Bird respirator and room air. Under sterile conditions, an incision was made in the fourth left intercostal space, and the pericardium was opened. Three experiments were carried out. Either the

trunk of the left coronary artery, or the left circumflex coronary artery and the left anterior descending coronary branches were ligated close to their origins, or the left circumflex coronary was ligated. An attempt was made to spare the septal branch of the left coronary artery in all experiments save where the main trunk of the left coronary artery was ligated.

Results: These are summarized in Table II. In all 3 groups, all test animals were given 100 units of somatotrophin 12 hours and 100 units 4 hours preoperatively by intramuscular injection. Control animals received saline injections. In some of the chronic studies, the animals were observed for 14 days and then sacrificed.

In Group I, the trunk of the left common coronary artery was ligated at its origin. In the control group of 3 animals, the average survival time was 3 minutes. In the treated group of 8 animals, the average survival time was 13 minutes.

TABLE II. SUMMARY OF DATA: CORONARY ARTERY LIGATIONS

	NUMBER OF DOGS	VENTRICULAR FIBRILLATION	RESUSCITATION	NUMBER SURVIVING/ TOTAL NUMBER		
				60 MIN.	24 HR.	14 DAYS
Occlusion of trunk of left common coronary artery						
Control	3	3 (survived 3 min.)				
Treated	8	8 (survived 13 min.)				
Occlusion of left anterior descending and left circumflex arteries						
Control	12	12	0 of 12 attempts	0	0	0
Treated	13	5	2 of 5 attempts	10/13	6/13	3/13
Occlusion of left circumflex artery						
Controls				15/28	10/28	6/17
Treated (50 u.)*				7/11	6/11	5/11
Treated (100 u.)				18/21	13/20	9/20
All treated				25/32	19/31	14/31

*These animals received 50 units of somatotrophin 12 hours and 4 hours, preoperatively.

In the second experimental group, the left anterior descending and the left circumflex coronary arteries were ligated close to their origins. It is seen that 12 out of 12 control animals showed ventricular fibrillation, and no attempts at resuscitation were successful. In the treated group of 13, on the other hand, only 5 exhibited immediate fibrillation and 2 of the 5 could be defibrillated by electrical shock. Since this procedure was found to be a rather severe one because of the marked hemodynamic changes incident to devascularization of the left ventricle, it was felt that a less severe test and one which would demonstrate the effects of somatotrophin on the fibrillatory threshold would be achieved by ligation of the left circumflex artery. In this third group, no attempts were made at defibrillation. Death during the first 24 hours can be attributed directly to fibrillation.

Protection by the hormone preparation was seen in all experiments. When the results were subjected to statistical analysis, using survival at 30 minutes, 1 hour, 24 hours, and 14 days, protection was found to be highly significant ($p<0.001$).

DISCUSSION

The increased irritability of the ventricles in the hypothermic dog has been observed by several groups of investigators.[1, 11, 12]

Swan and his co-workers[13] found that when dogs are cooled to a rectal temperature of 25° C. with inflow occlusion to the heart, many animals incurred ventricular fibrillation, especially when the occlusion of the venae cavae was released. The incidence of fibrillation was a function of ventilatory rate. In the hypoventilated animals, it was 50 per cent; in the hyperventilated group, 8 per cent. The only significant difference between these two groups was the blood pH. In both groups, the plasma potassium was consistently low. In the hypoventilated hypothermic dog, the renal excretion of potassium was several times greater than would be required to account for the loss of extracellular potassium, indicating a loss of intracellular potassium in the hypothermic animal with a low blood pH. It was concluded that hyperventilation was a successful method for reducing the incidence of fibrillation in the cold animal.

Another apparent relationship between fibrillation and potassium was demonstrated by Swan and his associates.[13] They found that the fibrillating hypothermic heart could rarely be converted to normal rhythm by massage combined with electric shock. However, with the method introduced in 1904 by D'Halluin[14] and studied by Hooker[15] according to which ventricular fibrillation is stopped with potassium chloride and regular contractions restored with calcium chloride, both drugs being perfused into the coronary arteries, they found that the fibrillation could usually be converted to normal rhythm directly or by the use of electrical shock. Fröhlicher,[16] in 1945, introduced the use of acetylcholine for defibrillating a mammalian heart. Fischer and Fröhlicher,[17] in 1948, successfully used adenosine triphosphoric acid (ATP). Montgomery and associates[9] demonstrated that Prostigmin has a marked antifibrillatory effect upon the ventricular myocardium of the hypothermic dog. The hypothermic myocardium during respiratory acidosis increases in potassium, while the opposite obtains during respiratory alkalosis, that is, potassium balance is maintained. During fibrillation the hypothermic myocardium loses potassium.

An experiment suggesting a relationship of potassium to fibrillation was carried out by Brown and Miller,[18] who found a high incidence of fibrillation in dogs suddenly changed from a breathing mixture containing a high concentration of carbon dioxide to room air. Similar experiments were carried out by Young, Sealy, Harris, and Botwin.[19] It was found that the serum potassium rose as the pH fell when the animals were being ventilated with 20 per cent carbon dioxide. When the animals had been breathing this gas mixture for 2 to 4 hours, they were suddenly allowed to breathe room air. This maneuver resulted in a rapid rise in pH, and the serum potassium at first rose suddenly to even higher levels before beginning to fall toward normal. The animals

incurred ventricular fibrillation during the time of the abrupt rise in serum potassium. The varied data summarized here suggest a relationship between the distribution of intra- and extracellular potassium and ventricular fibrillation. Somatotrophin has been demonstrated to be myoglycostatic; since the deposition and maintenance of glycogen stores entails stoichiometric quantities of potassium, such an agent might be important in maintaining a normal intracellular potassium balance. Such a function has been reported in the experimental hypothermic animal by Laborit and his co-workers.[20]

The results reported here show that premedication with somatotrophin of the hypothermic dog has a pronounced antifibrillatory effect. Further, in those instances in which fibrillation occurred, reversal of the fibrillation to a normal mechanism was accomplished in over one half of the attempts. This is in marked contrast to the ineffectiveness of resuscitation in the control animals. The fact that the incidence of ventricular fibrillation in hypothermia is significantly influenced by the anesthetic agent employed was demonstrated by Covino, Charleson, and D'Amato.[21] However, in our studies the same anesthetic agent was used throughout in comparable dosage.

Montgomery and associates[9] postulated that Adrenalin and sympathetic impulses to the heart might induce or potentiate ventricular fibrillation. Cahn and Melon,[22] in October, 1954, reported the use of Xylocaine blockade of the sinoauricular node to prevent ventricular fibrillation in dogs during hypothermia. Riberi, Siderys, and Shumacker[23] have recently reported on the effectiveness of this maneuver utilizing procaine. Shumacker and his associates[24] have shown that bilateral sympathetic denervation of the heart in hypothermic animals prevented fibrillation in all animals. Thus, interruption of nervous, precipitating factors may be as effective as measures directed to the metabolic level of the myocardium. Other techniques of accomplishing defibrillation have been well known for some time (Burmeister[25, 26]).

Ventricular ectopic activity following abrupt ligation of a coronary artery occurs in three phases (Harris,[27, 28] Beck[29]). The first phase has a duration of about 10 minutes. During this period ectopic activity develops in almost all animals and precipitates ventricular fibrillation in 30 per cent to 50 per cent of them. In the animals in which ventricular fibrillation does not develop, ectopic activity passes through a maximum and declines to reach a level of only an occasional premature beat or ceases completely within 20 minutes or less after occlusion. Throughout these experiments all ligations were performed in one stage to avoid the two-stage phenomena.

The second phase in the pattern of ectopic foci is a period of little or no ectopic activity following the first phase, or following a two-stage occlusion by-pass of the first stage. This period, during which there are only occasional ectopic activities, may have a duration of 4.5 to 8 hours, the average being 5 to 6 hours. With the introduction of the third phase there is a significant increase in the frequency of ectopic beats. The frequency of ectopic beats increases rapidly for the succeeding 4 hours, and then more slowly. Ventricular tachycardia of high frequency thus is produced and may obtain for 2 to 4 days. Necrosis of the myocardium begins simultaneously with the beginning of the third phase. The ligation of the left circumflex coronary artery was felt to

provide an adequate metabolic situation to induce fibrillation without inviting the more severe hemodynamic consequences of occlusion of the entire left coronary artery.

It is significant that the greatest degree of protection is seen in the periods of from 60 minutes to 24 hours following the ligation of the coronary vessels. This would appear to be explained by the metabolic events following the onset of myocardial necrosis.

In the protective action in hypothermic dogs and in dogs following ligations of coronary vessels, a certain latent period is necessary before any protection is achieved. The protective action apparently endures in the ligation experiments for at least 24 hours.

The mechanism of action of somatotrophin in producing these effects is unknown. It has been shown that the protein content in the bodies of hypophysectomized rats increases when the animals have received treatment with growth hormone (Li^{30}). Growth hormone is a powerful protein anabolic agent as demonstrated by experiments with sulfur-35-labeled albumin, in which the effect of growth hormone on the metabolism of plasma albumin was studied. It was found that growth hormone administered to the adult hypophysectomized rat produces an acceleration of albumin synthesis, increasing it by a factor of two or more (Ulrich[31]). Certain it is that intracellular potassium increases with protein deposition, and the rate of potassium mobility across cellular membranes may vary with intracellular protein. It may be that cardiac muscle, as Gerard[32] has shown for the central nervous system, does not depend on sugar and high-energy phosphate esters for quick energy release, but rather depends upon the breakdown of lipo- and nucleoprotein.

SUMMARY

1. In a significant number of cases premedication with somatotrophin prevents the ventricular fibrillation which regularly follows right ventriculotomy in the hypothermic dog.

2. In a series of dogs submitted to various types of coronary artery ligations, premedication with somatotrophin produced protection in all experiments to a highly significant degree ($p<0.001$).

3. Both in the hypothermic dogs and in those subjected to coronary artery ligations, a latent period is required before any protective effect may be demonstrated.

4. The mechanism of action of somatotrophin is unknown. All evidence points to activity on a cellular metabolic level.

REFERENCES

1. Bigelow, W. G., Lindsay, W. K., and Greenwood, W. F.: Hypothermia; Its Possible Role in Cardiac Surgery; An Investigation of Factors Governing Survival in Dogs at Low Body Temperatures, Ann. Surg. 132: 849, 1950.
2. Bigelow, W. G., Callaghan, J. C., and Hopps, J. A.: General Hypothermia for Experimental Intracardiac Surgery: Use of Electrophrenic Respirations, Artificial Pacemaker for Cardiac Standstill, and Radio-frequency Rewarming in General Hypothermia, Ann. Surg. 132: 531, 1950.
3. Senning, A.: Ventricular Fibrillation During Extracorporeal Circulation Used as a Method to Prevent Air Embolisms and to Facilitate Intracardiac Operations, Acta chir. scandinav. 171: 1, 1952.

4. Senning, A.: Ventricular Fibrillation During Hypothermia, Used as a Method to Facilitate Intracardiac Operations, Acta chir. scandinav. **109:** 303, 1955.
5. Helmsworth, J. A., Clark, L. C., Jr., Kaplan, S., and Ford, C.: A New Method for the Drainage of Blood From the Open Heart During Total By-pass of the Heart and Lungs, Surg. Forum: Clin. Congress Am. Coll. Surgeons **5:** 35, 1954.
6. Glenn, W. W. L., and Sewell, W. H., Jr.: Experimental Cardiac Surgery. IV. The Prevention of Air Embolism in Open Heart Surgery. Repair of Interauricular Septal Defects, Surgery **34:** 195, 1953.
7. Juvenelle, A., Lind, J., and Wegelius, C.: A New Method of Extracorporeal Circulation: Deep Hypothermia Combined With Artificial Circulation, Am. Heart J. **47:** 692, 1954.
8. Senning, A.: Extracorporeal Circulation Combined With Hypothermia, Acta chir. scandinav. **107:** 516, 1954.
9. Montgomery, A. V., Prevedel, A. E., and Swan, H.: Prostigmine Inhibition of Ventricular Fibrillation in the Hypothermic Dog, Circulation **10:** 721, 1954.
10. Harris, A. S., Bisteni, A., Russell, R. A., Brigham, J. C., and Firestone, J. E.: Excitatory Factors in Ventricular Tachycardia Resulting From Myocardial Ischemia; Potassium a Major Excitant, Science **119:** 200, 1954.
11. Hegnauer, A. H., D'Amato, H. D., and Flynn, J.: Influence of Intraventricular Catheters on the Course of Immersion Hypothermia in the Dog, Am. J. Physiol. **167:** 63, 1951.
12. Hoff, H. E., and Stansfield, H.: Ventricular Fibrillation Induced by Cold, Am. Heart J. **38:** 193, 1949.
13. Swan, H., Zeavin, I., Holmes, J. H., and Montgomery, V. H.: Cessation of Circulation in General Hypothermia. I. Physiologic Changes and Their Control, Ann. Surg. **138:** 360, 1953.
14. D'Halluin, M.: Le massage du coeur, Presse med., June, 1904, p. 346.
15. Hooker, D. R.: On Recovery of the Heart in Electric Shock, Am. J. Physiol. **91:** 305, 1929.
16. Fröhlicher, R.: Untersuchungen über die Wirkungen des Acetylcholine auf das elektrisch zum Flimmern gebrachte isolierte Säugetierherz, Helvet. physiol. et pharmacol. acta **3:** 230, 1945.
17. Fischer, H., and Fröhlicher, R.: Wiederherstellung des normalen Herzschlages nach elektrisch erzeugtem Kammerflimmern durch Adenosintriphosphorsäure (ATP). Experientia **4:** 155, 1948.
18. Brown, E. B., Jr., and Miller, F.: Ventricular Fibrillation Following a Rapid Fall in Alveolar Carbon Dioxide Concentration, Am. J. Physiol. **169:** 56, 1952.
19. Young, W. G., Jr., Sealy, W. C., Harris, J., and Botwin, A.: The Effect of Hypercapnia and Hypoxia on the Response of the Heart to Vagal Stimulation, Surg., Gynec. & Obst. **93:** 51, 1951.
20. Laborit, H., Jaulmes, C., and Kunlin, J.: Action d'un extrait somatotrope hypophysaire sur la fibrillation cardiaque en chirurgie experimentale, Presse med. **61:** 1537, 1953.
21. Covino, B. G., Charleson, D. A., and D'Amato, H. E.: Ventricular Fibrillation in the Hypothermic Dog, Am. J. Physiol. **178:** 148, 1954.
22. Cahn, J., and Melon, J. M.: Le coeur sous hibernation artificielle, Anesthesie, Par. **11:** 533, 1954.
23. Riberi, A., Siderys, H., and Shumacker, H. B., Jr.: Ventricular Fibrillation in the Hypothermic State. I. Prevention by Sino-auricular Node Blockade, Ann. Surg. **143:** 216, 1956.
24. Shumacker, H. B., Jr., Riberi, A., Boone, R. D., and Kajikuri, H.: Ventricular Fibrillation in the Hypothermic State. IV. The Role of Extrinsic Cardiac Innervation, Ann. Surg. **143:** 223, 1956.
25. Burmeister, H.: Tierexperimentelle Untersuchungen zur chemischen Behandlung des Kammerflimmerns, Wissenschaftliche Ztschr. Humboldt-Universität, Berlin **4:** 249, 1954.
26. Burmeister, H.: Experimenteller Beitrag zur Behandlung des Kammerflimmerns des Herzens bei Defibrillation mit chemischen Mitteln, Arch. klin. Chir. **281:** 225, 1955.
27. Harris, A. S.: Delayed Development of Ventricular Ectopic Rhythms Following Experimental Coronary Occlusion, Circulation **1:** 1318, 1950.
28. Harris, A. S., Estandia, A., and Tillotson, R. F.: Ventricular Ectopic Rhythms and Ventricular Fibrillation Following Cardiac Sympathectomy and Coronary Occlusion, Am. J. Physiol. **165:** 505, 1951.
29. Beck, C. S., and Leighninger, D. S.: Scientific Basis for the Surgical Treatment of Coronary Artery Disease, J. A. M. A. **159:** 1264, 1955.
30. Li, C. H., Geschwind, I. I., and Evans, H. M.: Effect of Growth Hormone on Inorganic Phosphorus Levels in Plasma, Endocrinology **44:** 67, 1949.
31. Ulrich, F., Tarver, H., and Li, C. H.: Effects of Growth and Adrenocorticotropic Hormones on the Metabolism of Albumin in Hypophysectomized Rats, J. Biol. Chem. **209:** 117, 1954.
32. Gerard, R. W.: Brain Fuel and Function, Science **123:** 673, 1956.

TOTAL BODY PERFUSION FOR OPEN CARDIOTOMY UTILIZING THE BUBBLE OXYGENATOR

Physiologic Responses in Man

Richard A. DeWall, M.D.* (by invitation), Herbert E. Warden, M.D.** (by invitation), Vincent L. Gott, M.D.*** (by invitation), Raymond C. Read, M.D. (by invitation), Richard L. Varco, M.D., and C. Walton Lillehei, M.D.
Minneapolis, Minn.

SINCE May, 1955, a simple disposable bubble[1, 2] oxygenator has been utilized together with a pump in 80 patients to permit intracardiac reparative surgery under direct vision by totally by-passing the heart and lungs. These patients have ranged in age from 4 weeks to 38 years and in weight from 2.6 Kg. to 56 Kg. A variety of thirteen types of congenital malformations or acquired cardiac lesions were found in these patients. The detailed considerations pertaining to these corrective procedures are the subject of other reports. Herein, it is our intention to present an analysis of the physiologic responses in the first 60 of these patients to their interval of total cardiopulmonary by-pass at various perfusion rates including observations upon acid-base alterations, oxygen consumption rates, effects upon the clotting mechanism, hemolysis, and arterial pressures.

Previous experience has indicated the usefulness of perfusions at flow rates considerably less than the full cardiac output[3-6] and in general this concept has been the basis for these procedures. Moreover, since the pump-oxygenator utilized in these operations has the capacity to provide any desired perfusion rate within the physiologic range, and inasmuch as an optimum perfusion rate for human beings is not known, these patients were perfused by intention at rates of flow varying from 26 to 60 c.c. per Kg. of body weight per minute to gain more objective data on this important consideration. The arterial perfusion rate selected for any given patient was maintained throughout the entire procedure, independent of occasional fluctuations of the venous return, by addition of blood to the extracorporeal circuit as needed. Consequently, the responses of the patients to a constant volume perfusion could be studied in relationship to that flow rate.

From The Department of Surgery and Variety Club Heart Hospital, University of Minnesota Medical School, Minneapolis 14, Minn.

Supported by Research Grants from: Graduate School, University of Minnesota; Life Insurance Medical Research Foundation; American Heart Association; Minnesota Heart Association; and National Heart Institute (H-830), United States Public Health Service.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

*Research Fellow, American Heart Association.

**Research Fellow, United States Public Health Service.

***National Heart Trainee, United States Public Health Service.

As total body perfusions often have been characterized by the development of blood acid-base alterations, our attention was directed particularly toward determining what factors contribute to these variations.

METHODS

One hundred per cent oxygen was used in the oxygenator to arterialize the venous blood, and the carbon dioxide was allowed to escape freely from the blood on the theory that a respiratory alkalosis would tend to counterbalance to some extent any tendency toward the development of a metabolic acidosis. The patient's control blood samples were drawn just before the perfusion after a period of controlled respiration with the chest open.

The biochemical data obtained have been grouped according to perfusion rates in order to define, if possible, an optimum flow rate, and also have been grouped according to whether cyanotic or acyanotic heart disease was present because of the substantial differences existing preoperatively in these two conditions.

To facilitate a comparison between perfusion rates and the development of acid-base alterations, plasma bicarbonate concentrations (alkaline reserve) have been determined. Values for pH alone are unreliable for a precise evaluation as the acid-base balance may vary widely without direct reflections on the pH due to compensation by the blood buffers. The differences in bicarbonate concentrations between the control values and test samples represent a quantitative determination of the alterations in the acid-base balance. To compare accurately these bicarbonate concentrations, the measured values for each patient need to be converted by calculation to a standard point of reference, a pH of 7.4 in these studies. The formula of Peters and Van Slyke[*7] was used for this calculation.

RESULTS

Acid-Base Changes During Total Body Perfusion.—

1. *In patients with acyanotic heart disease:* Table I illustrates the acid-base response to total body perfusion in 45 acyanotic patients studied. Control blood samples were not taken from the infants or small children; therefore complete determinations of the blood chemistry in the pre-perfusion state were available on only 10 patients. One may note from these data that all patients began the perfusion in a state of respiratory alkalosis as manifested by the elevated pH and depressed total CO_2 values. The final blood pH values measured at the conclusion of the perfusion interval were in the normal or near normal range for all of the perfusion rates studied. (Table I.) However, the differences between the control arterial bicarbonate levels calculated at pH 7.4, and the corresponding values at the termination of the by-pass indicate a

* $[HCO_3^-]\ pH\ 7.4 = [HCO_3^-]_{pH_x} - [(7.4 - pH_x)\ (8.2 + 2.3\ Hgb.)]$

Where:

$[HCO_3^-]\ pH\ 7.4$ = Plasma bicarbonate in mM/L. the sample at pH 7.4.

pH_x = Patient's measured hydrogen-ion concentration.

$[HCO_3^-]\ pH_x$ = Plasma bicarbonate at pH_x obtained from nomogram from patient's known pH_x and total CO_2 content or calculated from Henderson-Hesselbalch equation.

$(8.2 + 2.3\ Hgb.)$ = The slope of the buffer curve of whole blood with hemoglobin expressed as millimoles per liter which is $\frac{\text{Hgb. in Gms. \%}}{1.67}$

TABLE I. ACID-BASE RESPONSE TO TOTAL BODY PERFUSION IN PATIENTS WITH ACYANOTIC HEART DISEASE
(MEAN VALUES)

PERFUSION RATE C.C./KG./MIN.	NUMBER OF PATIENTS	MEAN DURATION OF BY-PASS (MIN.)
Group A: 30-35	23	17½
Group B: 36-41	10	16
Group C: 50-60	12	11½

	ARTERY				VEIN		
	pH	TOTAL CO_2† mM/L.	O_2 SATURATION (%)	PLASMA BICARBONATE‡ AT pH 7.4	HEMOGLOBIN (GM. %)	pH	TOTAL CO_2§ mM/L.	PLASMA BICARBONATE AT pH 7.4
Group A								
Control*	7.50	20.7	95	22.7	13.9	7.41	22.9	22.1
Defect corrected	7.33	17.7	95	14.7	14.7	7.24	22.9	16.8
By-pass concluded	7.34	17.4	95	15.6	14.8	7.24	20.7	14.8
15 min. after by-pass	7.36	18.2	95	16.1	14.8	--	--	--
Group B								
Control*	7.50	20.7	95	22.7	13.9	7.41	22.9	23.2
Defect corrected	--	--	--	--	14.9	7.29	24.0	19.2
By-pass concluded	7.34	18.5	96	15.8	14.9	7.29	21.6	16.9
15 min. after by-pass	7.34	19.3		16.6	14.9	--	--	--
Group C								
Control*	7.50	20.7	95	22.7	13.9	7.41	22.9	22.1
Defect corrected	--	--	--	--	15.0	7.30	22.8	19.6
By-pass concluded	7.45	15.8	96	16.5	15.0	7.32	21.4	17.8
15 min. after by-pass	7.39	18.9		17.7	15.0	--	--	--

*Samples taken just prior to by-pass.
†Normal value = 20-22.6 mM. per liter.[30]
‡See text for method of calculation.
§Normal value = 22.7-25.9 mM per liter.[30]

fall in the bicarbonate concentration for all three perfusion rates. The mean decrease in blood bicarbonate concentration was for Group A (30 to 35 c.c. per Kg. per min.), 66 mM per liter; for Group B (36 to 41 c.c. per Kg. per min.), 6.1 mM per liter; and for Group C (50 to 60 c.c. per Kg. per min.), 5.5 mM per liter.

Table II illustrates the duration of these perfusions. As one might anticipate that longer time intervals of perfusion would increase the bicarbonate depression, the change of bicarbonate concentration for each patient was plotted on a scattergram (Fig. 1) in relation to total duration of his perfusion. Fig. 1 indicates that the changes of bicarbonate concentration are widely variable, but suggests that Group C patients had less of a change than did the other groups. However, to assess this apparent difference more accurately, these patients need to be compared in relationship to the duration of

TABLE II. CLASSIFICATION OF PERTINENT DATA RELATING TO THE PERFUSIONS IN THE 60 PATIENTS STUDIED

PATIENT GROUP	TYPE OF HEART DISEASE	NUMBER PATIENTS	RANGE OF PERFUSIONS (C.C./KG./MIN.)	MEAN VALUES		
				PERFUSION FLOW RATE (C.C./KG./MIN.)	TIME OF CARDIAC DEFECT CORRECTION	TOTAL PERFUSION TIME
A	Acyanotic	23	30-35	31.5	9′ 30″	17′ 30″
B	Acyanotic	10	36-41	37.5	11″	16′ 0″
C	Acyanotic	12	50-60	52.5	8″	11′ 30″
D	Cyanotic	11	26-35	30.0	10′ 45″	25′ 3″
E	Cyanotic	4	40-50	45.0	13′ 45″	17′ 29″

their respective perfusions; therefore only those perfusions in Group A and Group B which lasted no longer than the perfusion of Group C were compared statistically to determine if there was any significant difference in the bicarbonate depression in these three groups. The differences observed in these three (flow rate) groups under this condition of comparable perfusion times were not significant; therefore one is unable to correlate significant changes in blood bicarbonate with these three different perfusion rates.

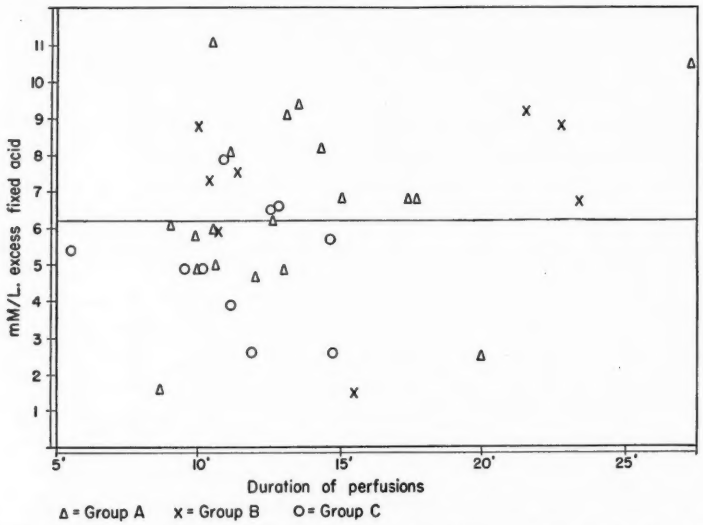


Fig. 1.—Relationship of plasma bicarbonate depression (accumulation of fixed acids) and duration of perfusion. (The solid line indicates the mean change.)

The patient's arterial samples taken about fifteen minutes after the termination of the perfusion indicate that the body mechanisms already had recovered as much as one mM per liter bicarbonate from their lowest levels toward their normal levels of 20 to 22.6 mM per liter (Table I).

2. *In patients with cyanotic heart disease:* In Table III is portrayed the acid-base balance of a group of patients with cyanotic heart disease sampled on the wards under ambulatory conditions without anesthesia and prior to corrective surgery. It may be noted from these data that all of the patients studied had reduced plasma bicarbonate levels. Moreover, in a number of these patients the fact that the arterial pH values were below normal levels indicates the existence of an uncompensated metabolic acidosis. Noteworthy, are the borderline and frankly elevated lactic acid values in these patients sampled under resting conditions.

The patients with cyanotic heart disease, as Table IV depicts, also developed a depression of their total bicarbonate during their perfusions, but the change from their control values was less than observed in the patients of Groups A, B, and C with acyanotic types of heart disease. In these cyanotic patients, their blood pH values were not significantly altered by the total bypass interval.

Lactic Acid Determinations.—Lactic acid determinations as a measure of fixed acids were made on a representative number of patients in each group. In each group, the lactic acid values at the conclusion of the by-pass averaged approximately two to three times the control value. The average final value for the acyanotic patients was 40 mg. per cent and for the cyanotic patients was 70 mg.

TABLE III. ALKALINE DEFICIT OF THE BLOOD OF PATIENTS WITH CONGENITAL CYANOTIC HEART DISEASE (PREOPERATIVE DATA)

	HEMOGLOBIN (GM. %)	ARTERIAL*			VENOUS*	
		pH_x	TOTAL CO_2 (mM/L.)	HCO_3^-§ AT pH 7.4	LACTIC‡ ACID (MG. %)	PLASMA CO_2 COMB. POWER IN MEQ./L.
J. O.†	11.6	7.32	22.7	19.6	104	24
S. S.	13.2	7.44	16.2	16.7	--	24
D. W.	13.1	7.40	18.4	18.4	20	21
M. W.	15.1	7.28	19.1	14.5	--	15
M. E.	17.3	7.44	21.9	22.3	12	16
C. S.	17.4	7.27	17.4	12.2	--	22
P. L.	16.9	7.33	15.6	12.6	--	18
E. B.	23.0	7.20	15.7	6.5	19	21
D. C.	24.0	7.43	14.0	15.2	20	22
J. A.	22.5	7.36	17.8	15.2	23	23
Mean values	17.4	7.35	17.9	15.3	33	20.6

*Blood samples drawn from ward patients without anesthesia under ambient conditions.
†Complete transposition of the great vessels, all others were patients with tetralogy of Fallot.
‡Normal value = 5 to 20 mg. per cent.
§Normal value = 20-22.6 mM per liter.

TABLE IV. ACID-BASE RESPONSE TO TOTAL BODY PERFUSION IN PATIENTS WITH CYANOTIC HEART DISEASE

PERFUSION RATE C.C./KG./MIN.	NUMBER OF PATIENTS	MEAN DURATION OF BY-PASS (MIN.)
Group D: 25-35	11	25.5
Group E: 40-50	4	17.5

	ARTERY			VEIN			
	pH	TOTAL CO_2 (mM/L.)	PLASMA BICARBONATE AT pH 7.4 IN mM/L.	HEMOGLOBIN (GM. %)	pH	TOTAL CO_2 (mM/L.)	PLASMA BICARBONATE AT pH 7.4 IN mM/L.
Group D							
*Control	7.35	17.9	15.2	14.9	7.37	20.6	18.6
Defect corrected	--	--	--	14.7	7.22	24.2	19.3
By-pass concluded	7.36	14.7	11.9	15.7	7.23	18.8	12.4
15 min. after by-pass	7.38	16.0	14.6	15.1	--	--	--
Group E							
Defect corrected	--	--	--	15.4	7.26	21.4	16.0
By-pass concluded	7.35	14.2	12.4	15.4	7.26	19.2	13.9
15 min. after by-pass	7.28	15.3	11.0	15.4	--	--	--

*Represents controls for both Groups D and E.

per cent. The cyanotic patients began their perfusions with considerably elevated blood levels of lactic acid in some instances as Table III indicates. These values may be compared with normal values of 5 to 20 mg. per cent and values of 100 mg. per cent observed in athletes after competition such as a basketball game.

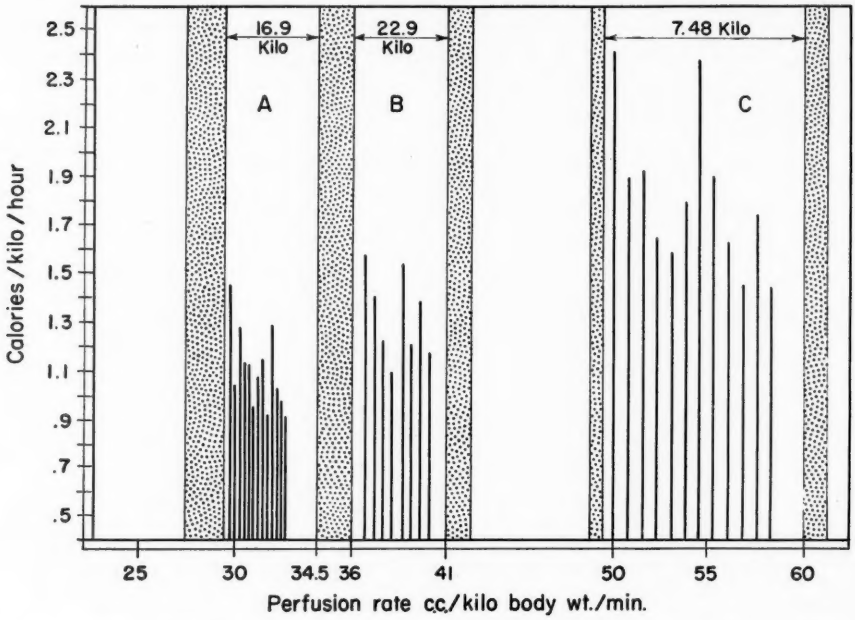


Fig. 2.—Oxygen consumption rates during total body perfusion in patients with acyanotic heart disease. Mean body weights for each group are indicated.

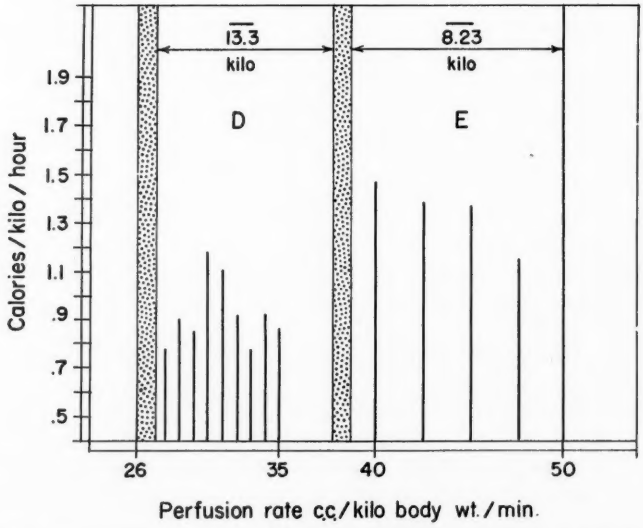


Fig. 3.—Oxygen consumption rates during total body perfusion in patients with cyanotic heart disease. Mean body weights for each group are indicated.

Oxygen Consumption Rates.—Oxygen consumption rates during the by-pass interval were calculated for each group of patients. These values, as calories used per kilogram of body weight per hour, are summarized in Fig. 2 for the acyanotic patients and in Fig. 3 for the cyanotic patients. This calculation was made by taking the difference between the arterial and venous oxygen content at the time the defect was corrected. At this time the patient was still totally supported by the oxygenator and the venous blood had reached maximum desaturation. Since the patient's perfusion rates or "cardiac output" were known and constant, the total quantity of oxygen used by the patient per minute could be readily calculated. The basal respiratory quotient[8] of 0.82 was selected for the conversion factor of oxygen into calories, the value of which is 4.825 calories per liter of oxygen. Temperature also affects oxygen consumption and, as the heart tolerates surgery upon itself better at normal temperatures, these patients were maintained euthermic throughout the procedure by the addition of heat as necessary from an electric blanket under the patients and from the constant temperature water bath in which the oxygenator reservoir was mounted.

As the age and the weight of the patient are directly correlated with the oxygen consumption rate these values for each group have been plotted individually in Figs. 2 and 3, with the smallest patient in each group plotted to the left of the next larger-sized patient. As can be noted, the smaller the patient in each group the higher the oxygen consumption rate per kilogram of body weight, and Group C, which represents the smallest patients in this series, had the highest oxygen consumption rates. It can be noted that the cyanotic patients over-all had a lower oxygen consumption rate than did the acyanotic patients. Table V also illustrates this in that the cyanotic patients did not desaturate their venous blood to the same degree as the acyanotic patients at comparable perfusion rates.

TABLE V. MAXIMUM DESATURATION OF POOLED VENOUS BLOOD SAMPLES* MEASURED DURING PERFUSION (VENOUS O_2 CONTENT AT TIME DEFECT CLOSED)

	ACYANOTIC PATIENTS			CYANOTIC PATIENTS	
	A	B	C	D	E
Perfusion rate (c.c./Kg./min.)	30-35	36-41	50-60	26-35	40-50
O_2 content (vol. per cent)	7.1	7.5	6.6	8.5	8.8
Per cent saturated	36.0	39.0	34.0	43.0	43.0

*Sampled from the patients' caval catheters.

Effect of the Pump-Oxygenator Upon Blood Elements.—For many of the cases the perfusion apparatus was primed with freshly drawn arterialized venous blood[9] in heparin.* This blood closely approximates normal arterial blood in pH, CO_2 content, hemoglobin, and oxygen saturation. In other patients, priming was carried out by arterializing freshly drawn heparinized venous blood by passage through the oxygenator to fill the helix reservoir.

Hemolysis.—The apparatus used in these patients produced a degree of hemolysis well within the range considered innocuous. There was often a direct relationship of hemolysis to duration of the perfusion, but the mean

*18 mg. per 500 c.c. bottle.

value for hemolysis did not vary in any definite manner in the various groups in relationship to perfusion rates. The mean hemolysis for all the cases was 33 mg. per cent plasma hemoglobin with a range from a low of 6 mg. per cent to a high of 80 mg. per cent.

Clotting mechanism: Platelet counts in this entire group of 80 patients averaged 266,000 per cubic millimeters preoperatively, the mean value for the determination made within two hours after the perfusion was 200,000 per cubic millimeters. The bleeding times preoperatively averaged four and one-half minutes and were the same for the determinations made within two hours after the perfusion. The control clotting times on these patients was four minutes, forty-five seconds with a five-minute clotting time as the mean value within two hours after the perfusion. Table VI summarizes these data.

TABLE VI. EFFECT OF TOTAL BY-PASS PERFUSIONS WITH PUMP-OXYGENATOR UPON THE CLOTTING ELEMENTS (MEAN VALUES FOR 80 PATIENTS)

	PLATELETS (CU. MM.)	BLEEDING TIME (MIN.)	CLOTTING TIME (MIN.)
Preoperative	266,000	4′ 30″	4′ 45″
Postperfusion*	200,000	4′ 30″	5′

*All determinations made within two hours after conclusion of actual perfusion.

Pressure Measurements.—In 2 adult patients continuous intraluminal arterial pressures were monitered throughout the perfusion. One patient with a ventricular septal defect, who received a perfusion rate of 34 c.c. per Kg. of body weight per minute, maintained a systolic arterial pressure of 75 mm. Hg or more throughout the entire procedure. The other patient with an aortic stenosis, perfused at 32 c.c. per Kg. per minute, maintained a systolic arterial pressure of 70 mm. Hg or better except for a short interval after the corrective procedure when the clamp which occluded the aorta was released at which time her pressure momentarily fell to 30 mm. Hg. Recovery in both patients was uneventful.

COMMENT

The oxygenator herein employed has proved to be efficient in the performance of the respiratory functions for these patients during their interval of total pulmonary by-pass. At all flow rates the oxygenation of the venous blood by this oxygenator was optimal (95 to 96 per cent) for perfusion of the arterial system (Table I). Moreover, the carbon dioxide content of the arterial blood returning to the patient from the oxygenator was consistently less than the control or normal values, indicating that this apparatus adequately removed the carbon dioxide of catabolism from the venous blood. This lowered arterial carbon dioxide content may be readily altered to normal by the simple addition of some carbon dioxide to the oxygenating gases. In this regard we have generally felt that some degree of carbon dioxide content depression was desirable in these patients to oppose the metabolic acidosis generally occurring in patients undergoing anesthesia and major surgical procedures.

However, recent investigations have indicated that the arterial carbon dioxide content is the principal humoral agent controlling the vasomotor tone

in the cerebral circulation in man. In this regard, Gibbs and his associates,[10] and Kety and Schmidt[11] have pointed out that depressed arterial carbon dioxide levels decreased and high levels increased the cerebral blood flow. They also state that cerebral oxygen consumption was unchanged by the various concentrations of arterial carbon dioxide studied.

The patients herein studied undergoing total body perfusion utilizing the pump-oxygenator invariably awakened immediately postanesthesia and appeared mentally alert and were completely free of any evidence of neurologic sequelae related to their perfusion interval. However, despite these gratifying clinical observations indicating the gross adequacy of the cerebral flow during the perfusions, it is of obvious importance to study more precisely the effects of various flow rates and of various partial pressures of arterial carbon dioxide in the perfusing blood utilizing electroencephalography to evaluate cerebral function. These studies are currently in progress.

In assessing acid-base balance in these patients no chemical means were used during or immediately after the by-pass interval to counteract fluctuations in hydrogen-ion concentration. Thus, the observed data represent the patient's own reponses to perfusion and surgery influenced only by the above-mentioned respiratory alkalosis. In regard to acid-base balance, it is worthy of emphasis that blood pH values alone result in an incomplete picture inasmuch as they may be normal or even on the alkaline side of normal despite a gain of fixed acids in the blood. For this reason, the alterations in response to perfusion in the total plasma bicarbonate, as a measure of the alkaline reserve, have been determined in these patients. All of our patients manifested a depression of their total plasma bicarbonate as a result of their interval of perfusion. This depression was due to an accumulation of fixed acids and can otherwise be expressed as the development of a compensated metabolic acidosis. All of our patients had mild elevations in blood lactate, but levels well below those found during exercise.[20, 21] The range of bicarbonate deficit developed in these patients varied from 3.3 mM per liter in the cyanotic group patients (Group D) to 6.7 mM per liter in the acyanotic patients (Group A). The normal daily variations in fixed acids have been reported to range from 2.7 mM per liter[12] to 4.0 mM per liter while values as high as 9.3 mM per liter have been found to occur during pulmonary surgery.[13]

A gain in fixed acids averaging 5.2 mM per liter has been found in children less than one year of age receiving ether anesthesia for general surgical procedures of only moderate magnitude such as herniorrhaphy or pyloromyotomy.[14] In 27 older children, undergoing similar type surgical procedures, the gain in fixed acids averaged 4.0 mM per liter. These authors concluded that a moderate acidosis of this degree was not harmful and of no practical significance. The same authors[14] presented evidence that this gain in fixed acids was due to the sympathomimetic effect of ether upon the adrenal medulla augmented in some of their patients by the intravenous administration of glucose and/or blood, both of which increase the fixed acid content of the patient. The injection of epinephrine alone is known to produce marked elevations of fixed acids.[19]

In our patients, ether anesthesia was not utilized (cyclopropane, Pentothal sodium, oxygen) but there were numerous other sympathomimetic stimuli acting in these patients, principal of which were apprehension immediately prior to and during the induction of anesthesia in the children and older patients as well as the lowered systemic blood pressure during the perfusion interval in all patients. Thus, in our patients there are at least two possible etiologic factors that could account for the gain in fixed acids observed. These are stimulation of the sympathetic nervous system and adrenal medulla, or tissue hypoxia. In attempting to assess the relative importance of these two etiological factors serum potassium determinations have been helpful. Serial serum potassium determinations were made on many of our patients[15] and in none did the serum potassium rise, but decreased appreciably in every instance. Several investigators have observed that hypoxia produces an elevation of the serum potassium,[16, 17] while epinephrine effect decreases the serum potassium.[18]

This evidence, presented together with the fact that in the larger acyanotic patient group approximately the same degree of metabolic acidosis occurred regardless of the different perfusion rates employed, has led us to believe that the bicarbonate depression found in our patients was primarily an epinephrine effect.

Moreover, it is evident that in the series of patients herein studied, undergoing a bilateral thoracotomy and surgical procedures of considerably greater magnitude and duration including an interval of total body perfusion as well as multiple blood transfusions, did not develop accumulations of fixed acids appreciably different from those observed in the above-mentioned series of relatively minor operations.

This finding together with such other observations as the fact that the newborn infant customarily begins life in a state of uncompensated metabolic acidosis,[22] and that similar degrees of acidosis are the normal consequence of exercise[20, 21] have led us to believe that the degree of bicarbonate depression (without significant alteration in pH) observed in our patients was probably of no practical significance and supports our clinical impression that acidosis per se has not been the cause of any difficulty.

Obviously, this conclusion, based upon intracardiac operations of relatively short duration, may not necessarily hold for the future inasmuch as perfusion intervals of several hours or more may be desirable for performance of more complicated procedures. In such occasional patients it may be necessary to control the acidosis by pumping the full basal cardiac output which imposes technical difficulties of a substantial nature in regard to cannulations, or possibly by the interposition of an artificial kidney in the extracorporeal circuit.

Bing,[23] Morse,[24] and their associates have observed bicarbonate levels below normal and decreased arterial carbon dioxide tensions in many patients with cyanotic heart disease. Morse noted that this was due to an excess of fixed acids or a combination of fixed acid excess or CO_2 deficit. We have confirmed these observations especially in the more seriously incapacitated

cyanotic patients. This consideration poses a question at present unanswerable as to the ability of these patients in all instances to readjust promptly and without difficulty to the more normal values resulting directly and inexorably from the anatomic and physiologic correction of their circulation.

Normal oxygen consumption rates have been given[25] as varying from 2.5 calories per Kg. of body weight per hour for infants to 1.43 calories per Kg. of body weight per hour for older children. Another author[23] gives the range of 2.3 calories per Kg. of body weight per hour to 1.05 calories per Kg. of body weight per hour from infancy to maturity. All of our patients received sodium thiopental anesthesia, which has been found to reduce oxygen consumption by as much as 20 per cent.[27] Moreover, cyanotic patients are known to have decreased basal metabolic rates by as much as 24 per cent below normal. The reduced oxygen consumption rates as compared to normal values that were observed in these patients would appear to be within a range accountable for entirely on the basis of the known depression[27] of oxygen consumption with anesthesia augmented by the further decrease associated with cyanotic heart disease.[28]

The clotting abnormalities frequently present preoperatively in cyanotic patients are generally appreciated. Surprising has been the finding that approximately one third of the patients with acyanotic heart disease[29] also have measurable defects preoperatively in their clotting mechanisms. These have been manifested by prolonged bleeding and clotting times, prolonged prothrombin times, and increased prothrombin consumption times. These clotting defects have not imposed any contraindications to surgery, and in fact the clotting mechanism in many of these patients has been better in the immediate postoperative period than that existing preoperatively.

Hemolysis during these perfusions has been of no significance while bleeding and clotting times return rapidly to normal after the perfusion. There was no detectable relationship between perfusion rate and mortality in this series. This is not surprising since survival following the corrective procedures has been more directly related to the cardiac reserve of the patient, the severity of the pulmonary hypertension where present, and technical problems involved in the reparative surgery.

SUMMARY

Open intracardiac reparative procedures have been performed on 80 patients with the use of a pump-oxygenator. The biochemical responses to total body perfusion in the first 60 of these patients with either acyanotic or cyanotic heart disease have been studied. Arterial and venous blood pH, carbon dioxide contents, oxygen contents, and hemoglobin measurements have been determined before, during, and after the perfusions in these patients to assess acid-base equilibria in relationship to various perfusion rates. In many patients blood lactic-acid levels were determined also.

During total body perfusion, a moderate plasma bicarbonate depression regularly occurred (mean fall in corrected bicarbonate varying from 3.3 mM per liter in 15 patients with cyanotic heart disease to 6.0 mM per liter in the 45 pa-

tients with acyanotic forms of heart disease). This depression was accompanied by a moderate elevation of blood lactic acid in almost all patients in which this measurement was made. Values for pH did not vary greatly from normal. Serum potassium values regularly decreased moderately during the perfusions.

These changes in bicarbonate, lactic acid, and potassium occurring during total body perfusion are qualitatively and quantitatively similar to the changes observed during the administration of epinephrine in physiologic quantities. It is believed that these changes in acid-base equilibria are the result of a reflex stimulation of the sympathetic nervous system rather than tissue hypoxia. No relationship was observed between this moderate bicarbonate depression and postoperative morbidity and mortality in this series of patients.

Preoperatively all patients with cyanotic heart disease were found to be in a state of metabolic acidosis under ambulatory conditions.

The smaller and younger patients had higher oxygen consumption rates during the perfusion as they do in normal states, therefore, they should receive higher perfusion rates than older children and adults during their procedures.

Hemolysis of the blood during the perfusion was minimal.

Platelet, bleeding, and clotting times were not greatly different in the pre- and postoperative periods.

We wish to express our appreciation to Dr. E. B. Brown of the Department of Physiology, University of Minnesota for his aid in the interpretation of the biochemical data presented. We also extend our thanks to Mr. Eugene Johnson of the Department of Biostatistics for his aid in the statistical interpretation of portions of these data.

REFERENCES

1. Lillehei, C. W., DeWall, R. A., Read, R. C., Warden, H. E., and Varco, R. L.: Direct Vision Intracardiac Surgery in Man Using a Simple Disposable Artificial Oxygenator, Dis. Chest **24**: 1-8, 1956.
2. DeWall, R. A., Warden, H. E., Read, R. C., Gott, V. L., Ziegler, N., Varco, R. L., and Lillehei, C. W.: A Simple Expendable Artificial Oxygenator for Open Heart Surgery, Surg. Clin. North America **36**: 1025-1034, 1956.
3. Cohen, M., and Lillehei, C. W.: A Quantitative Study of the "Azygos Factor" During Vena Caval Occlusion in the Dog, Surg., Gynec. & Obst. **98**: 225-232, 1954.
4. Cohen, M., Warden, H. E., and Lillehei, C. W.: Physiologic and Metabolic Changes During Autogenous Lobe Oxygenation With Total Cardiac By-Pass Employing the Azygos Flow Principle, Surg., Gynec. & Obst. **98**: 523-529, 1954.
5. Warden, H. E., Cohen, M., Read, R. C., and Lillehei, C. W.: Controlled Cross Circulation for Open Intracardiac Surgery, J. THORACIC SURG. **28**: 331-343, 1954.
6. Lillehei, C. W., Cohen, M., Warden, H. E., and Varco, R. L.: The Direct Vision Intracardiac Correction of Congenital Anomalies by Controlled Cross Circulation: Results in Thirty-Two Patients With Ventricular Septal Defects, Tetralogy of Fallot and Atrioventricularis Communis Defects, Surgery **38**: 11-29, 1955.
7. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, 1931, Vol. 1, Chapter 18, Williams & Wilkins Company, vol. 1, p. 912.
8. Best, C., and Taylor, N.: The Physiological Basis of Medical Practice. Metabolism and Nutrition, ed. 5, Williams & Wilkins Company, pp. 607-622, Baltimore, 1950.
9. Warden, H. E., Read, R. C., DeWall, R. A., Aust, J. B., Cohen, M., Ziegler, N. R., Varco, R. L., and Lillehei, C. W.: Direct Vision Intracardiac Surgery by Means of a Reservoir of "Arterialized Venous" Blood, J. THORACIC SURG. **30**: 649-657, 1955.
10. Gibbs, F. A., Maxwell, H., and Gibbs, E. L.: Volume Flow of Blood Through the Human Brain, Arch. Neurol. Psychiat. **57**: 137-144, 1948.

11. Kety, S. S., and Schmidt, C. F.: The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption in Normal Young Men, J. Clin. Invest. **27**: 484-492, 1948.
12. Gibbon, J. H., Allbritten, F. F., Jr., Stayman, J. W., Jr., and Judd, J. M.: A Clinical Study of Respiratory Exchange During Prolonged Operations With an Open Thorax, Ann. Surg. **132**: 611-625, 1950.
13. Beecher, H. K., and Murphy, A. J.: Acidosis During Thoracic Surgery, J. THORACIC SURG. **19**: 50-70, 1950.
14. Bunker, J. P., Brewster, W. R., Smith, R. M., and Beecher, H. K.: Metabolic Effects of Anesthesia in Man: III. Acid-Base Balance in Infants and Children During Anesthesia, J. Appl. Physiol. **5**: 233-241, 1952.
15. DeWall, R. A., Warden, H. E., Melby, V. C., Minot, H., Varco, R. L., and Lillehei, C. W.: Total Body Perfusion With a Pump Oxygenator for Open Intracardiac Surgery: Physiologic Responses in 120 Patients, Proc. Surg. Forum, Clin. Congress, Am. Coll. Surgeons, Philadelphia, 1956, W. B. Saunders Company, vol. 7.
16. Mullin, F. J., Dennis, J., and Calvin, D. B.: Blood Potassium in Tetany and Asphyxia of Dogs, Am. J. Physiol. **124**: 192-201, 1938.
17. Cattell, McKeen, and Civin, H.: The Influence of Asphyxia and Other Factors on the Serum Potassium of Cats, J. Biol. Chem. **126**: 633-643, 1938.
18. Brewer, G., Larson, P. S., and Schroeder, A. R.: On the Effect of Epinephrine on Blood Potassium, Am. J. Physiol. **126**: 708-712, 1938.
19. Griffith, F. R., Lockwood, J. E., and Emery, F. E.: Adrenalin Lactacidemia: Proportionality With Dose, Am. J. Physiol. **127**: 415-421, 1939.
20. Lipmann, F. (After O. Bang): A Symposium on Respiratory Enzymes, Madison, 1942, University of Wisconsin Press.
21. Friedemann, T. E., and Barborka, C. J.: The Significance of the Ratio of Lactic to Pyruvic Acid in the Blood After Exercise, J. Biol. Chem. **141**: 993, 1941.
22. Kaiser, I. H.: Some Observations on the Fetus in Utero, Med. Bull. Univ. Minnesota **27**: 6, 1956.
23. Bing, R. J., Vandam, L. D., Andelsman, H., Campbell, J. C., Spencer, J. A., and Griswold, H. E.: Physiological Studies in Congenital Heart Disease. VI. Adaptations to Anoxia in Congenital Heart Disease with Cyanosis, Bull. Johns Hopkins Hosp. **83**: 439-446, 1948.
24. Morse, M., and Cassels, D. E.: Arterial Blood Gases and Acid Base Balance in Cyanotic Congenital Heart Disease, J. Clin. Invest. **32**: 837-846, 1953.
25. Lewis, R. C., Kinsman, G., and Iliff, A.: The Basal Metabolism of Normal Boys and Girls From Two to Twelve Years Old Inclusive, Am. J. Dis. Child. **53**: 348-428, 1937.
26. Hansen, A.: Nutritional Requirements and Digestion. Mitchell-Nelson Textbook of Pediatrics, ed. 5, Philadelphia, 1950, W. B. Saunders Company, pp. 87-121.
27. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics, ed. 2, New York, 1955, The Macmillan Company, chap. 9.
28. Bing, R. J., Vandam, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease: II. Results of Preoperative Studies in Patients With Tetralogy of Fallot, Bull. Johns Hopkins Hosp. **80**: 121, 1947.
29. Krivit, W.: Deficiencies of the Blood Clotting Mechanism in Patients With Acyanotic Congenital Heart Disease, in preparation.
30. Gibbs, E. L., Lennox, W. D., Nims, L. F., and Gibbs, F. A.: Arterial and Cerebral Venous Blood-Arterial Venous Differences in Man, J. Biol. Chem. **144**: 325-332, 1942.

A METHOD FOR CONTROLLED CARDIAC ARREST AS AN ADJUNCT TO OPEN HEART SURGERY

W. GLENN YOUNG, JR., M.D. (BY INVITATION), WILL C. SEALY, M.D., IVAN W. BROWN, JR., M.D. (BY INVITATION), WILMER C. HEWITT, JR., M.D. (BY INVITATION), HENRY A. CALLAWAY, JR., M.D. (BY INVITATION), DORIS H. MERRITT, M.D. (BY INVITATION), AND JEROME S. HARRIS, M.D. (BY INVITATION)
DURHAM, N. C.

AS experimental and clinical evidence accumulates, it is becoming apparent that the unhurried and precise repair of many intracardiac defects will require the use of a mechanical pump and oxygenator. Maintenance of the coronary and systemic circulation for short periods can be achieved safely with reduced flow rates as shown by Lillehei and his associates.[1] The addition of hypothermia to this technique would appear desirable if the danger of irreversible cardiac arrhythmias during ventriculotomy can be eliminated.

When cardiotomy is performed during arterial perfusion, however, blood loss through the coronary sinus and regurgitation through the aortic valve may be profuse and would make direct procedures on the aortic valve or within the left ventricle almost impossible. This difficulty can be overcome by occluding the ascending aorta in addition to the venae cavae, thus rendering the heart totally ischemic. The contracting, normothermic heart can safely withstand this maneuver only one to 3 minutes.[1, 2] Hypothermia to 25° C. apparently increases this safe time limit only slightly; to 5 or 6 minutes.[3, 4]

Induced cardiac arrest by decreasing cardiac metabolism would theoretically allow more prolonged aortic and coronary occlusion. The advantages of a dry, motionless operative field free from danger of air embolism are apparent.

It has been known since the time of Ringer[5] that an excess of potassium ion in the coronary circulation will cause the heart to stop in diastole. Hooker,[6] Wiggers,[7] and more recently Swan[2] have injected potassium salts into the heart to stop ventricular fibrillation. Senning[8] attempted to temporarily inhibit the cardiac contractions by injections of potassium chloride, acetylcholine, Mecholyl, and related compounds but was unsuccessful apparently because he maintained coronary perfusion and immediately washed out or diluted the cardioplegic agent. His technique of initiating fibrillation prior to cardiotomy is helpful in preventing air embolism but would not theoretically allow prolonged inflow and outflow occlusion because the metabolism of the fibrillating heart may actually be higher than normal.[9, 10]

From the Division of Thoracic Surgery and Departments of Pediatrics and Biochemistry, Duke University School of Medicine, Durham, N. C.

This investigation was supported in part by a research grant (H-1782 C) from the National Heart Institute of the National Institutes of Health, Public Health Service. A portion of these studies was carried out under contract beween Duke University and the United States Atomic Energy Commission.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

Lam and co-workers[11] have reported the induction of cardiac arrest in hypothermic dogs by intraventricular injection of 5 per cent potassium chloride with survival after complete circulatory occlusion up to 30 minutes. In their experiments, restoration of normal rhythm was accomplished by cardiac massage and was apparently preceded routinely by ventricular fibrillation which required countershocks. In England, Melrose and his associates[12] have also reported preliminary experiments using potassium citrate to temporarily arrest cardiac action in isolated hearts and in the intact animal.

In studies to be reported elsewhere,[13] a search was made for a more satisfactory cardioplegic agent. Such an agent should show the following characteristics: (1) rapid induction of complete cardiac arrest, (2) complete lack of electrical and muscular cardiac activity during the cardioplegia, (3) rapid resumption of a normal cardiac beat on re-perfusion of the coronary vessels with blood, (4) absence of ventricular fibrillation, and (5) absence of toxicity if the entire dose gained entrance to the general circulation.

Various drugs and mixtures were tested by injection into the coronary perfusion system of isolated cat hearts in a Langendorff perfusion apparatus.[14] If cardiac arrest resulted, the perfusion was stopped for 10 minutes. The time required for resumption of normal beat on re-perfusion with a modified Ringer-Locke solution was noted, together with the type of electrocardiographic and muscular activity regained.

Briefly, it was found (Table I) that both potassium citrate and magnesium sulfate alone produced rapid cardiac arrest. The incidence of fibrillation following administration of the magnesium salt alone, however, made this drug undesirable. By combining the two agents, fibrillation was usually avoided and the concentration and quantity of potassium citrate could be reduced.

TABLE I. INDUCED CARDIAC ARREST IN THE ISOLATED CAT HEART

SOLUTION INJECTED (10 ML.)	NUMBER OF TRIALS	AVERAGE TIME TO ARREST BEAT (MIN.)	TIME TO RESUME BEAT* (MIN.)	INCIDENCE OF FIBRILLATION
K. Cit. 1.6 per cent	5	0.6	2.1	0
$MgSO_4$ 3.69 per cent	7	1.2	1.2	3
†K. Cit.-$MgSO_4$	13	0.3	1.7	2
†K. Cit.-$MgSO_4$ + 10 mg. Benadryl	7	1.0	1.7	0
†K. Cit.-$MgSO_4$ + 12.5 mg. Pyribenzamine	7	1.0	1.9	0
†K. Cit.-$MgSO_4$ + 0.5 mg. Prostigmin	7	0.6	3.5	0

*All hearts cardioplegic for ten minutes. No appreciable change from original electrocardiogram pattern after good beat established.

†0.54 Gm. potassium citrate and 2.47 Gm. magnesium sulfate per 100 ml.; adjusted to pH 7.4 with sodium bicarbonate. (200 meq./L. magnesium and 50 meq./L. potassium.)

Using these data, a basic solution was evolved containing 2.47 Gm. per cent magnesium sulfate ($MgSO_4 \cdot 7H_2O$) and 0.54 Gm. per cent potassium citrate [$K_3(C_6H_5O_7) \cdot H_2O$] brought to pH 7.4 with sodium bicarbonate. The addition of small quantities of Prostigmin or one of the antihistaminics[15] seemed to

further decrease the incidence of fibrillation in the isolated cat heart. The bradycardia produced by Prostigmin also theoretically decreases metabolism during the critical period after resumption of cardiac activity.

The results were then applied to a series of normothermic and hypothermic dogs undergoing right ventriculotomy with inflow and outflow tract occlusion for varying periods of time.

EXPERIMENTAL DATA

Methods.—Prior to each experiment, 100 ml. of the magnesium sulfate-potassium citrate solution was prepared and the pH adjusted to 7.4 with sodium bicarbonate. In the majority of instances, Prostigmin (1 mg. per 100 ml.) was added to the solution.

Dogs weighing 9 to 20 Kg. were anesthetized with sodium pentobarbital (30 mg. per Kg.) and artificial respiration begun at a rate to ensure moderate hyperventilation. When hypothermia was desired, this was accomplished by immersion in ice water. Rectal temperatures in the hypothermic animals ranged from 24°-28° C. The right chest was entered and the azygos vein ligated. Tourniquets were placed about the venae cavae and through the transverse pericardial sinus about the aorta and pulmonary artery. A purse-string suture of fine silk was placed in the adventitia of the proximal aorta in order to prevent bleeding from the injection site. As the inflow and outflow tourniquets were tightened the cardioplegic solution was rapidly injected into the aorta through a No. 20 needle with a slightly curved tip. Care was taken that the needle tip remained distal to the aortic valve cusps. The injection was continued until all visible cardiac contractions ceased and the heart failed to respond to mechanical stimulation of the ventricle. The needle was then withdrawn and the hemostatic suture tied. With the heart motionless and empty, right ventriculotomy was performed and repaired in a leisurely fashion.

After completing the cardiotomy, the outflow tourniquet was loosened and coronary perfusion resumed. In the acute experiments to be discussed, the brain was protected by hypothermia during the period of circulatory arrest and the cardioplegic solution washed out with oxygenated Ringer's solution introduced under pressure through a Foley-type catheter in the subclavian and brachiocephalic artery. During this period of time, the right auricle was opened to allow egress of the perfusion fluid and prevent overdilatation of the heart. When satisfactory cardiac rhythm resumed, the coronary circulation was primed with oxygenated blood through the catheter, and the venae cavae opened slowly. After removing the catheter, the animal was observed for varying periods of time.

Physiologic studies undertaken during these experiments included electrocardiography, femoral arterial blood pressures, and determinations of blood pH, sodium, potassium, magnesium, chloride, and carbon dioxide.

More recently using a simple extracorporeal pump-oxygenator system[16] to maintain the systemic circulation, cardiac activity was restored simply by releasing the outflow tourniquet and allowing coronary perfusion to resume with oxygenated blood.

RESULTS

Fourteen acute experiments were performed on hypothermic dogs, each undergoing right ventriculotomy. One and six-tenths per cent potassium citrate was used to induce cardiac arrest in 6 of the animals and the potassium citrate-magnesium sulfate-Prostigmin mixture in eight of the experiments. The quantity of drug injected averaged 21 c.c. for potassium citrate and 24 c.c. in the potassium-magnesium-Prostigmin group. Duration of complete cardiac ischemia (outflow occlusion) ranged from 6 to 14 minutes (average 9.4 minutes). Resumption of regular cardiac rhythm occurred in 13 of the animals following coronary perfusion with Ringer's solution. Ventricular fibrillation developed in the first experiment when difficulty with the perfusion catheter occurred and resuscitation was attempted by cardiac massage. Two of the dogs (both in the potassium citrate group) subsequently developed ventricular fibrillation prior to completing the operative procedure. This low incidence of fibrillation in the hypothermic animals seemed quite remarkable to us considering the crude method of coronary perfusion and the surgical manipulations undertaken.

The time required for return of a satisfactory heartbeat in these experiments ranged from 2 to 10 minutes (average 4.7 minutes). The 11 dogs surviving the operative procedure maintained a satisfactory blood pressure and electrocardiographic pattern until sacrificed 30 minutes to 9 hours later. To test the toxicity of the solution, 3 of these animals were given a second injection of the cardioplegic agent rapidly by systemic vein during the observation period. Except for a temporary fall in blood pressure and bradycardia, this injection was tolerated well.

Survival experiments performed in combination with the pump-oxygenator system have confirmed our initial impression of the feasibility of this technique. The ease of resuming coronary perfusion by simply releasing the aortic tourniquet greatly simplifies the procedure, and no other resuscitative efforts are necessary. Table II summarizes the results in ten experiments employing the pump-oxygenator and one in which coronary perfusion was re-established with Ringer's solution under sterile conditions. The longest period of total inflow and outflow occlusion without serious arrhythmia and with long-term survival has been 21 minutes. The upper limits of tolerance have not been established as yet. From these early observations, it appears that the time required to resume normal cardiac activity is directly proportional to the duration of ischemia, but the factor of coronary flow rates may be significant. During this interval, support of the systemic and coronary circulations must be accomplished by the artificial heart-lung apparatus. Although normal cardiac rhythm was re-established in all animals, deaths occurred in several due to secondary hypotension or failure to regain consciousness. This mortality has been attributed to prolonged extracorporeal circulation at flow rates which are now considered inadequate.

Electrocardiographic tracings of one of the surviving dogs are depicted in Fig. 1. After 11 minutes of complete ischemia, the heart showed a fairly normal electrocardiogram within one minute after resuming coronary perfusion.

TABLE II. RESULTS IN DOGS UNDERGOING RIGHT VENTRICULOTOMY DURING INDUCED CARDIAC ARREST

WEIGHT OF DOG (Kg.)	LOWEST TEMPERATURE (° C.)	SOLUTION* INJECTED	AORTIC OCCLUSION (MIN.)	TIME TO GOOD BEAT (MIN.)	VENTRICULAR FIBRILLATION	MAXIMUM SERUM LEVEL MEQ./L.		COMMENT
						POTASSIUM	MAGNESIUM	
9.1	24	30 c.c. K-M-P	6.5	8	0	3.9	4.8	Fibrillation 100 min. later during secondary hypotension
18.0†	27	15 c.c. 1.6 % K. Cit.	8.0	3	0	5.0	--	Recovery
9.3	27	10 c.c. K-M-P	9.0	2	0	5.9	3.0	Died 7 hours later; failed to regain consciousness
8.4	26	25 c.c. K-M-P	10.0	9	0	5.9	6.0	Recovery
8.0	27	45 c.c. K-M-P	21.0	16	0	6.1	4.8	Recovery
13.0	34	30 c.c. K-M-P	5.0	1	0	4.3	2.1	Died of hemorrhage 8 hours later
14.0	31	60 c.c. K-M-P	8.0	11	Transient (air embolus)	4.3	4.7	Recovery
9.4	32	35 c.c. K-M-P	10.0	1	0	3.2	2.4	Lived 24 hours with brain damage
9.0	32	25 c.c. K-M-P	10.0	1	0	5.1	6.1	Died 5 hours later; hypotension and brain damage
15.0	31	30 c.c. K-M-P	11.0	1	0	4.6	5.1	Recovery
11.0	34	50 c.c. K-M-P	12.5	12	0	5.2	4.2	Secondary hypotension 2½ hours after procedure with death

*K-M-P refers to potassium citrate-magnesium sulfate-Prostigmin mixture (see text).
†Coronary perfusion re-established with Ringer's solution.

In other experiments, varying degrees of auricular-ventricular block with bizarre QRS complexes were noted during the recovery period. These conduction disturbances vanished as the perfusion continued and the potassium and magnesium of the cardioplegic solution were washed away.

Elevation of serum potassium and magnesium was minimal despite the fact that no especial effort had been made to prevent entry of the cardioplegic solution into the general circulation in many of these experiments. The highest potassium and magnesium levels noted following resumption of cardiac activity are not within the generally accepted toxic range.

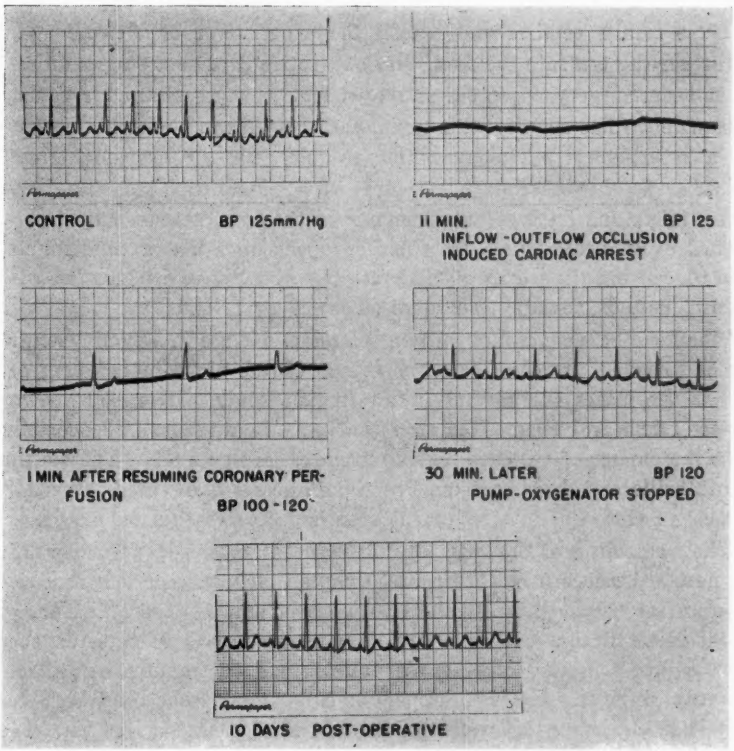


Fig. 1.—Electrocardiogram (Lead II) of dog undergoing right ventriculotomy with controlled cardiac arrest.

The blood entering the right auricle during coronary perfusion but prior to resumption of cardiac activity appeared well saturated with oxygen. Although no definite conclusion concerning the oxygen consumption of cardiac muscle during induced arrest can be made without flow measurements, the marked decrease in femoral arterial-coronary sinus oxygen difference as determined in seven experiments seems significant (Table III).

TABLE III. FEMORAL ARTERIAL-CORONARY SINUS OXYGEN DIFFERENCES (VOLS. %)

EXPERIMENT NUMBER	1	2	3	4	5	6	7	AVERAGE
Inflow occlusion; heart beating; perfusion with pump-oxygenator before cardiac arrest	62.0	47.3	10.3	50.0	59.2	14.4	47.5	41.5
Inflow occlusion; immediately after resumption of coronary perfusion but prior to return of heartbeat	5.4	2.3	5.4	4.7	7.5	0.0	0.0	3.6

DISCUSSION

These results confirm and extend the experiments of Melrose and Lam and further demonstrate the feasibility of elective cardiac arrest as an adjunct in open-heart surgery. Because of the variable time necessary for resumption of adequate cardiac activity, this technique must always be used in conjunction with a satisfactory pump-oxygenator to maintain the systemic circulation whether or not hypothermia is present. It is noteworthy that the danger of serious arrhythmia during ventriculotomy in the hypothermic animal is almost abolished by this technique. This finding opens up a new avenue for investigation concerning the merits of moderate hypothermia in conjunction with the low flow pump-oxygenator techniques advanced by Lillehei.

Whether the magnesium sulfate-potassium citrate-Prostigmin solution is superior to potassium chloride or potassium citrate alone in inducing cardiac arrest in the intact animal must await further study. It is well known that both potassium and magnesium stop the heart in diastole. The combination lessens the danger of systemic toxicity from either one alone. The addition of an antifibrillatory drug such as Prostigmin seems warranted, especially, as previously mentioned, in view of the resultant bradycardia on recovery.

The metabolism of the heart during induced arrest appears to be different from normal because it can withstand complete ischemia for longer periods of time than the beating heart without apparent damage. The maximum period of total inflow-outflow occlusion with long-term survival in these experiments was 21 minutes in the hypothermic animals and 11 minutes in animals not previously refrigerated. The upper limit of total ischemia which can be tolerated safely using this technique has not been established as yet. Rohde[17] found that the metabolism of the arrested heart was less than one half that of the normally contracting heart. The results of our determinations of arteriovenous oxygen difference are suggestive of a marked decrease in metabolism during arrest. This problem is being investigated further.

SUMMARY

Following experiments on the isolated cat heart, controlled cardiac arrest, using a solution of magnesium sulfate and potassium citrate, was induced in a group of normothermic and hypothermic dogs undergoing right ventricu-

lotomy. It was found that this technique is feasible in allowing recovery after prolonged periods of complete cessation of the coronary circulation and in preventing serious arrhythmias during cardiotomy.

The application of this method to cardiac surgery is discussed.

ADDENDUM

This method of controlled cardiac arrest has been used in 2 patients operated upon with temperatures of 30° C. and 31° C., respectively. Normal heart action returned in both. One case, a 2-week-old infant, died because of an irreparable anomaly an hour after induced standstill. The other, a 7-year-old boy who had both ventricular and auricular septal defects closed, survived twenty-three minutes of extracorporeal circulation and seventeen minutes of cardiac standstill. Though he regained consciousness and had normal blood pressure, he died twelve hours later from the results of irreversible vascular changes in the lung.

REFERENCES

1. Lillehei, C. W., Cohen, M., Warden, H. E., and Varco, R. L.: The Direct-Vision Intracardiac Correction of Congenital Anomalies by Controlled Cross Circulation, Surgery **38**: 11, 1955.
2. Swan, H., and Zeavin, I.: Cessation of Circulation in General Hypothermia. III. Technics of Intracardiac Surgery Under Direct Vision, Ann. Surg. **139**: 385, 1954.
3. Scott, H. W., Collins, H. A., and Foster, J. H.: Hypothermia as an Adjuvant in Cardiovascular Surgery: Experimental and Clinical Observations, Am. Surgeon **20**: 799, 1954.
4. Edwards, W. S., Simmons, E., Lombardo, C. R., Bennett, A., and Bing, R. J.: Coronary Blood Flow in Hypothermia, Arch. Surg. **71**: 853, 1955.
5. Ringer, S.: The Influence of Certain Blood Constituents on the Heart, J. Physiol. **4**: 29, 1883.
6. Hooker, D. R.: On the Recovery of the Heart in Electric Shock, Am. J. Physiol. **91**: 305, 1929.
7. Wiggers, C. J.: Studies of Ventricular Fibrillation Caused by Electric Shock, Am. J. Physiol. **93**: 197, 1930.
8. Senning, A.: Ventricular Fibrillation During Extracorporeal Circulation, Acta chir. scandinav. suppl. 171, 1952.
9. Gregg, D. E.: Coronary Circulation in Health and Disease, Philadelphia, 1950, Lea & Febiger.
10. Jardetzky, O., Greene, E. A., and Lorber, V.: Oxygen Consumption of the Completely Isolated Dog Heart in Fibrillation, Circulation Res. **4**: 144, 1956.
11. Lam, C. R., Geoghegan, T., and Lepore, A.: Induced Cardiac Arrest for Intracardiac Surgical Procedures, J. THORACIC SURG. **30**: 620, 1955.
12. Melrose, D. B., Dreyer, B., Bentall, H. H., and Baker, J. B. E.: Elective Cardiac Arrest, Lancet **2**: 21, 1955.
13. Merritt, D. H., Sealy, W. C., Young, W. G., and Harris, J. S.: Evaluation of Cardioplegic Drugs for Surgery Using Isolated Perfused Cat Heart. To be published.
14. Langendorff, O.: Untersuchungen am überlebenden Saugethierherzen, Pflug. Arch. **61**: 291, 1895.
15. Dipalma, J. R., and Schults, J. E.: Antifibrillatory Drugs, Medicine **29**: 123, 1950.
16. Brown, I. W., Hewitt, W. C., Young, W. G., and Sealy, W. C.: A Simple Expendable Blood Oxygen-Gas Exchanger for Use in Open Cardiac Surgery, Surgery **40**: 100, 1956.
17. Rohde: Quoted by Gregg.[9]

THE NEUTRALIZATION OF HEPARIN BY PROTAMINE IN EXTRACORPOREAL CIRCULATION

RAYMOND HURT, M.B., F.R.C.S.* (BY INVITATION), HERBERT A. PERKINS, M.D. (BY INVITATION), JOHN J. OSBORN, M.D. (BY INVITATION), AND FRANK GERBODE, M.D.
SAN FRANCISCO, CALIF.

AT THE conclusion of a heart-lung by-pass with an extracorporeal circulation, it is necessary to neutralize the anticoagulant action of the heparin with protamine. If this is not done adequately, continued hemorrhage will occur and lead to an extensive hemothorax. During the course of studies in extracorporeal circulation in dogs, it became apparent that the protamine itself may cause several side effects; it may cause an increase in the clotting time if given in excess, it may cause a shocklike syndrome, or it may cause a thrombocytopenia. At the conclusion of the by-pass, it is therefore important to avoid an overdose of protamine, and to give only sufficient to neutralize the heparin that is circulating in the blood at that time. A method of protamine titration has been developed in order to estimate the correct dose, and it is the purpose of this paper to describe this method of protamine titration briefly, and then to present data which demonstrate some of the undesirable side effects of the intravenous injection of protamine.

A METHOD OF PROTAMINE TITRATION

It is difficult to estimate the correct dose of protamine for the following reasons: (1) The dose of protamine required to neutralize heparin in vivo is not the same dose as is required for its neutralization in vitro, (2) preparations of heparin and protamine vary greatly in their effect and, (3) the quantity of protamine required to neutralize a given dose of heparin will decrease with increasing time from the point of heparin injection. Therefore, a method of protamine titration in vivo has been developed in order to estimate the required dose.

The method is briefly as follows: The protamine that is to be used subsequently is set up in 11 small tubes in concentrations of from zero to 50 meg. in a volume of 0.1 ml. One milliliter of blood is added to each tube, which is inverted once to mix its contents. The tubes are inspected at the end of 15 minutes to see which have clotted. The dose of protamine required to neutralize the

From the Departments of Surgery and Medicine, Stanford University School of Medicine, San Francisco, Calif.

Aided by grants from the United States Public Health Service and the American Heart Association.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

*Traveling Fellow of The American Association for Thoracic Surgery.

heparin in the circulating blood is then calculated by taking the concentration of protamine in the tube that has clotted with the least amount of protamine and multiplying this concentration by the estimated blood volume of the dog (Fig. 1).

This method of protamine titration[1] has demonstrated that in the past a considerable excess of protamine has often been given. It has also shown how easy it is to prolong the clotting time of the blood by a relatively small overdose of protamine.

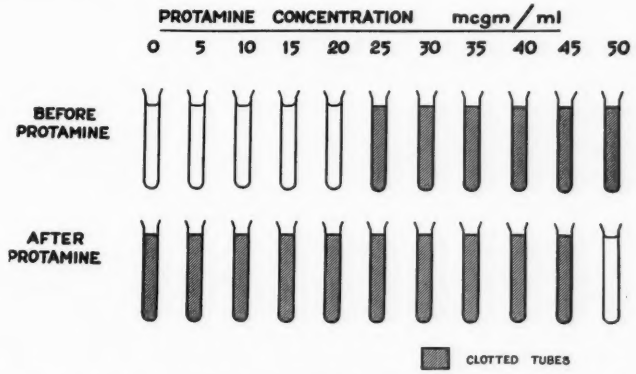


Fig. 1.—An example of a protamine titration. The upper row of tubes shows that a clot formed in those which contained protamine in concentrations greater than 25 micrograms per milliliter. The dose of protamine required by the dog can be estimated by the method described in the text.

The lower row of tubes demonstrates a second confirmatory titration, and shows how an excess of protamine in the tube at the extreme right prevented the formation of any clot.

THE EFFECT OF EXTRACORPOREAL CIRCULATION ON PROTAMINE SHOCK

The occurrence of a toxic reaction following the rapid intravenous injection of protamine was reported by Japelli[2] and subsequently by others workers.[3-7] This toxic reaction is manifest by a fall in blood pressure and an increase in the depth and rate of respiration. When it occurs at the conclusion of a heart-lung by-pass the animal may pass into a state of shock from which it may never recover. However, the reaction is very variable and depends on the species of animal, the dose of protamine, and even on whether or not the animal is anesthetized. In the dog, for example, 2 mg. protamine per kilogram of body weight will result in a temporary fall in blood pressure if the animal is anesthetized, whereas the same dose to an unanesthetized animal will cause no reaction. The reports of different workers are contradictory, however, and this may be accounted for by a difference in the source, and therefore the method of manufacture, of the protamine.

Despite these variable and, at times, conflicting reports, it appeared that the reaction which followed the injection of protamine into the normal dog was very much less severe than that which so often occurred following its use at the conclusion of a heart-lung by-pass with an extracorporeal pump-oxygenator. It is known that there may be considerable damage to the blood during its passage through an extracorporeal circuit and it was thought that this

might have some connection with the occurrence of a more severe reaction to the protamine. In fact, the severity of the reaction might be an indication of the extent of such damage.

In order to ascertain whether or not this was true, a study was made of the effect of an intravenous injection of a standard dose of protamine into normal heparinized dogs. This was compared to the effect of a comparable dose of protamine into dogs whose blood had been passed through an extracorporeal pump.

METHOD

Adult mongrel dogs weighing between 6 and 11.5 Kg. were used. They were anesthetized with intravenous Nembutal, 30 mg. per kilogram of body weight.

Effect of Protamine on Normal Dogs.—Heparin (Upjohn heparin sodium, 10 mg. per milliliter) was given intravenously in a dose of 2 mg. per kilogram body weight. Forty-five minutes later an approximately neutralizing dose of protamine, 1 mg. protamine per milligram heparin (Eli Lilly protamine sulphate, 1 per cent), was injected intravenously over a period of about 3 seconds and the effect on the blood pressure and pulse rate noted on a continuously recording oscillograph.

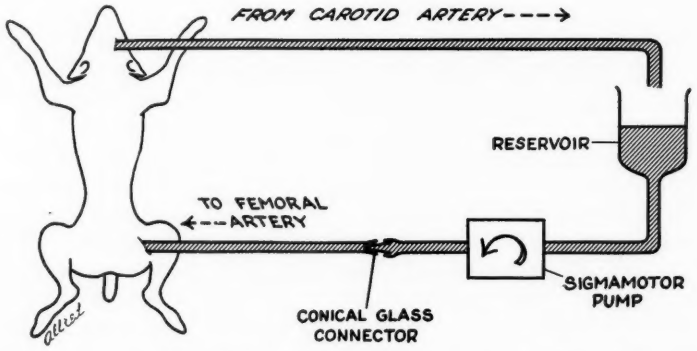


Fig. 2.—Schematic diagram of the apparatus used to produce a traumatic perfusion.

Effect of Protamine on Dogs Whose Blood Had Been Damaged by Passage Through an Extracorporeal Pump.—Heparin was given intravenously to these dogs in a similar dose to that used in the normal animals. The pump system that was used to traumatize the blood is shown diagrammatically in Fig. 2. Blood from the carotid artery was collected in a reservoir from which it was pumped back into the femoral artery by a Sigmamotor pump. In order to increase the resistance against which the pump had to work and so produce an adequate amount of damage to the blood, a conical glass connecting piece was inserted in the circuit between the pump and the femoral artery. The rate of flow was 250 to 480 ml. per minute and the time of perfusion was 30 to 45 minutes. Five minutes after the perfusion was completed the appropriate dose of protamine

was given intravenously over a period of 3 seconds and the effect on the blood pressure and pulse rate noted as before. The degree of damage to the blood was assessed by plasma hemoglobin estimations at intervals during the course of the perfusion.

RESULTS

Effect on Normal Dogs.—Observations were made on 12 dogs. A typical response to the intravenous injection of protamine (in a dosage of 2 mg. per kilogram of body weight) is shown in Fig. 3. About 25 seconds after the injection, there was a sudden fall in blood pressure from 200/160 to 130/80 mm. Hg lasting for 6 seconds, following which it gradually rose to its original level in 18 seconds. This type of response was obtained in 9 dogs. The blood pressure remained low for 6 to 20 seconds and returned to normal in 15 to 50 seconds. In some cases, there was also a definite bradycardia lasting for up to 15 seconds (Fig. 4). This may be called a normal reaction in an unperfused dog.

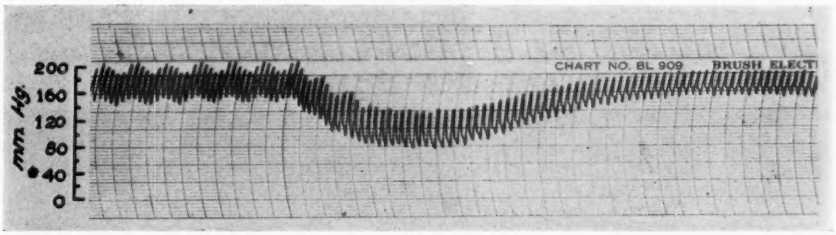


Fig. 3.—A typical protamine reaction in a normal dog, showing the brief duration of the hypotension.

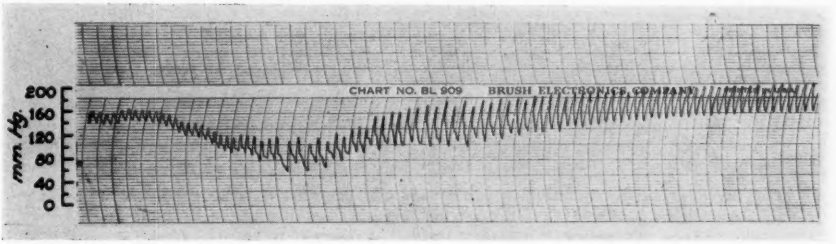


Fig. 4.—A protamine reaction in a normal dog, showing a transitory bradycardia.

In 3 dogs the reaction was more severe. The blood pressure remained low for one-half to 2 minutes and did not return to normal for 2 to 5 minutes. The fall in blood pressure was accompanied by a slight but definite bradycardia.

Effect on Perfused Dogs.—Observations were made on 14 dogs. The degree of hemolysis produced by the Sigmamotor pump varied between 10 and 24 mg. hemoglobin per cent after a perfusion lasting 30 minutes, and between 20 and 78 mg. hemoglobin per cent after a perfusion lasting 45 minutes, except in one case in which there was an extreme degree of hemolysis of 1,440 mg.

hemoglobin per cent. A typical reaction to the intravenous injection of the protamine is shown in Fig. 5. About 30 seconds after the injection there was a sudden fall in blood pressure from 180/140 to 100/80 mm. Hg lasting for 2 minutes, following which it gradually rose until it was back to normal in 8 minutes. In some cases, especially those in which there was a less prolonged fall in blood pressure, there was a very definite bradycardia which persisted for several minutes after the blood pressure had returned to normal (Fig. 6).

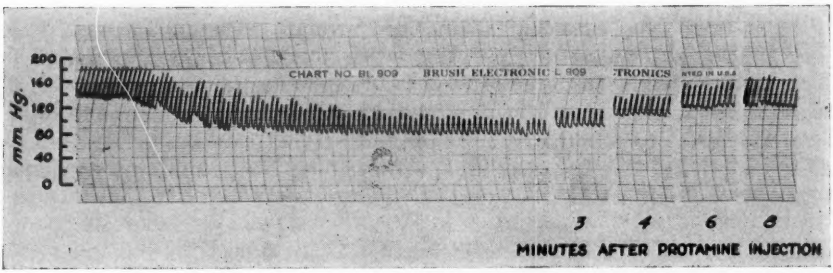


Fig. 5.—A typical protamine reaction in a perfused dog, showing a prolonged period of hypotension.

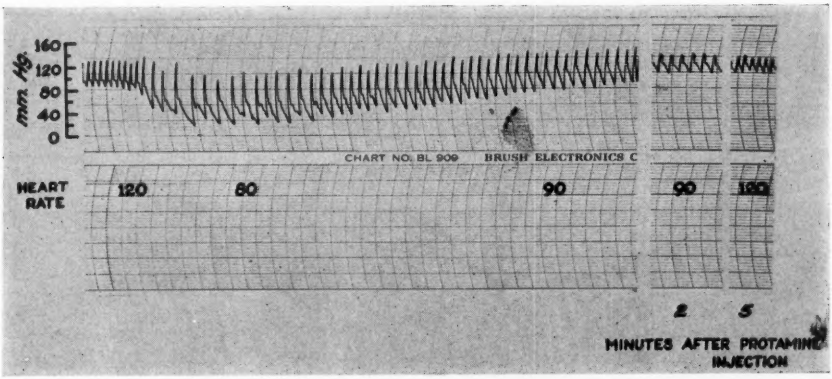


Fig. 6.—A protamine reaction in a perfused dog, showing a period of bradycardia.

These two types of severe reaction were obtained in 9 dogs; in 7 the blood pressure remained low for one-half to 16 minutes and did not return to normal for 2 to 26 minutes, while in 2 the fall was within the limits of a normal response in an unperfused dog, but none the less a very marked bradycardia developed, lasting for 2 and 5 minutes, respectively.

A slight reaction resembling that already described as the normal response in an unperfused dog occurred in 3 cases. The blood pressure remained low for 5 to 15 seconds and returned to normal in 15 to 40 seconds.

A more marked reaction, but one that was not sufficiently great to be classified as severe, was obtained in 2 dogs.

A statistical analysis of these results (using Kendall's ι for tied ranks[9]) shows that they are significant (significance at 2 per cent level) and that a severe reaction occurred more frequently in the case of the perfused dogs.

DISCUSSION

The rapid injection of protamine intravenously has been shown to cause a pronounced fall in blood pressure, the severity of which depends on whether or not the blood has been damaged by passage through an extracorporeal circuit. It may also cause a very definite bradycardia, both in the normal and in the perfused dog. The duration of this bradycardia is variable; it may last for only a few seconds, even though the blood pressure is still low, or it may last for several minutes after the blood pressure has returned to its original level. The severity of the bradycardia is independent of the change in blood pressure and it would therefore appear likely that they are not associated. This is in agreement with Jaques' view[6] that the fall in blood pressure is due to an arteriolar dilatation since the physiologic effect of such a change would be a quickening rather than a slowing of the pulse rate. As far as is known, this bradycardia has not previously been reported as part of the toxic reaction to protamine.

The severity of the reaction to protamine does not appear to correspond to the degree of damage to the blood as judged by plasma hemoglobin estimations though, of course, this estimation only measures one aspect of blood damage. It is interesting to note that in the one case in which the blood was intentionally damaged very severely (plasma hemoglobin of 1,440 mg. per cent after 45 minutes) there was a fall in blood pressure lasting only 15 seconds.

The results of the investigation are summarized in Table I which shows that 9 out of the 14 perfused dogs (64.3 per cent) developed a severe reaction, as compared with 3 out of the 12 unperfused dogs (25 per cent). These results are statistically significant and show that the severe reaction occurred more commonly in the perfused dogs.

TABLE I

REACTION	NORMAL DOGS	PERFUSED DOGS
Slight	9	3
Moderate	0	2
Severe	3	9
Total	12	14

Protamine is probably less toxic to man than it is to dogs[6, 8] but nevertheless it is possible that a more severe reaction might occur following the administration of protamine at the conclusion of a heart-lung by-pass in human beings. The effect of the consequent hypotension and bradycardia would be exaggerated by the open thoracotomy and might well weigh heavily against the survival of the patient.

As the reaction is likely to be less severe if the protamine is given slowly, it is considered advisable for the drug to be given over a period of several minutes.

TABLE II. THE EFFECT OF PROTAMINE ON NORMAL DOGS

DOG NO.	FALL IN BLOOD PRESSURE (MM. HG) FROM	TO	TIME OF MAIN FALL IN BLOOD PRESSURE	TIME UNTIL NORMAL BLOOD PRESSURE	BRADYCARDIA*	REACTION
1	200/160	130/80	6 sec.	18 sec.	0	Slight
7	200/130	120/50	2 min.	4 min.	+	Severe
8	180/100	140/60	10 sec.	20 sec.	0	Slight
11	140/90	90/40	12 sec.	20 sec.	0	Slight
12	160/120	120/80	18 sec.	25 sec.	0	Slight
19	140/100	60/40	20 sec.	50 sec.	0	Slight
20	160/120	100/60	10 sec.	40 sec.	0	Slight
21	180/140	100/70	30 sec.	2 min.	+	Severe
22	160/120	40/10	30 sec.	5 min.	+	Severe
23	180/120	110/70	15 sec.	45 sec.	0	Slight
24	140/100	80/40	10 sec.	50 sec.	0	Slight
26	160/100	100/60	15 sec.	40 sec.	0	Slight

*Bradycardia: + = lasted for 1 minute or less.

TABLE III. THE EFFECT OF PROTAMINE ON PERFUSED DOGS

DOG NO.	TIME OF PERFUSION (MIN.)	PLASMA HGB. AFTER PERFUSION (MG. %)	FALL IN BLOOD PRESSURE (MM. HG) FROM	TO	TIME OF MAIN FALL IN BLOOD PRESSURE	TIME UNTIL NORMAL BLOOD PRESSURE	BRADYCARDIA*	REACTION
2	30	10	180/130	150/60	5 sec.	15 sec.	++++	Severe
3	30	18	140/100	80/50	16 min.	26 min.	+	Severe
4	30	22	190/140	160/70	10 sec.	30 sec.	+	Intermediate
5	30	24	200/150	150/100	10 sec.	30 sec.	0	Slight
6	30	10	200/130	120/50	30 sec.	80 sec.	+	Intermediate
9	45	1440	180/?	100/?	5 sec.	15 sec.	0	Slight
10	45	25	180/140	100/80	2 min.	8 min.	0	Severe
13	45	25	180/130	130/100	50 sec.	5 min.	0	Severe
14	45	31	140/100	90/70	30 sec.	2 min.	++++	Severe
15	45	20	140/100	100/60	15 sec.	40 sec.	+	Slight
16	45	32	160/?	80/?	2 min.	7 min.	0	Severe
17	45	78	180/110	80/20	10 sec.	20 sec.	++	Severe
18	45	36	160/100	80/30	1½ min.	10 min.	+	Severe
25	45	40	150/100	80/40	2 min.	11 min.	+	Severe

*Bradycardia: ++++ = lasted for 5 minutes.
++ = lasted for 2 minutes.
+ = lasted for 1 minute or less.

THE EFFECT OF PROTAMINE ON PLATELETS

In seven of the above experiments, platelet counts were carried out immediately before and, at short intervals, after the injection of the protamine. In each case there was a marked fall in the platelet count, the severity of which correlated well with the degree of shock produced. This thrombocytopenia following the administration of protamine was demonstrated by Jaques,[6] in 1949. It is not known whether the fall in platelet count is the cause or the result of the drop in blood pressure, but further investigations are in progress to elucidate this point.

SUMMARY

A method of protamine titration has been described by which it is possible to estimate the correct dose of protamine at the conclusion of a heart-lung by-pass.

A study has been made of the effect of the intravenous injection of a standard dose of protamine (2 mg. per kilogram of body weight) on normal dogs, and also on dogs whose blood has been damaged by passage through an extracorporeal circuit.

The protamine has been found to cause a fall in blood pressure and a bradycardia which occur independently of each other. The severity of the reaction is variable, but is much more marked in those dogs whose blood has been damaged by passage through an extracorporeal circuit.

The effect of protamine on platelets is briefly discussed.

REFERENCES

1. Perkins, H. A., Osborn, J. J., Hurt, R., and Gerbode, F.: Neutralization of Heparin in Vivo With Protamine; A Simple Method of Estimating the Required Dose, J. Clin. & Lab. Med. **48**: 223, 1956.
2. Japelli, A.: Boll. Soc. ital. Biol. sper. **8**: 778, 1933.
3. Jaques, L. B., Charles, A. F., and Best, C. H.: Administration of Heparin, Acta med. scandinav., suppl. **90**: 190, 1938.
4. Shelley, W. B., Hodgkins, M. P., and Visscher, M. B.: Studies on the Toxicity of Protamine, Proc. Soc. Exper. Biol. & Med. **50**: 300, 1942.
5. Vartiainen, I., and Marble, A.: The Effect of the Subcutaneous Administration of Protamine (Salmine) to Rabbits and Mice, J. Lab. & Clin. Med. **26**: 1416, 1941.
6. Jaques, L. B.: A Study of the Toxicity of the Protamine (Salmine), Brit. J. Pharmacol. **4**: 135, 1949.
7. Parkin, T. W., and Kvale, W. F.: Neutralization of the Anticoagulant Effects of Heparin With Protamine (Salmine), Am. Heart J. **37**: 333, 1949.
8. Quick, A. J., Shanberge, J. N., and Stefanini, M.: Effect of Heparin on Platelets in Vivo, J. Lab. & Clin. Med. **33**: 1424, 1948.
9. Kendall, M. G.: Rank Correlation Methods, London, 1948, Griffin Company, chap. 4.

DISPOSABLE MEMBRANE OXYGENATOR (HEART-LUNG MACHINE) AND ITS USE IN EXPERIMENTAL SURGERY

DONALD B. EFFLER, M.D., WILLEM J. KOLFF, M.D. (BY INVITATION), LAURENCE K. GROVES, M.D. (BY INVITATION), AND F. MASON SONES, JR., M.D. (BY INVITATION)
CLEVELAND, OHIO

INTRODUCTION

OPERATIONS in the open heart at normal body temperature require heart-lung machines as a substitute for cardiopulmonary function (Fig. 1). It was believed for a long time that the machine would have to pump and oxygenate blood in amounts equal to the normal resting cardiac output—at least 100 ml. per kilogram of body weight per minute. However, Andreasen and Watson[1, 2] in England have shown that dogs survived at least 35 minutes of occlusion of both venae cavae when only the azygos vein was left open and cardiac output was reduced to 10 to 18 ml. per kilogram of body weight per minute. Lillehei, Varco, and co-workers[3-7] have greatly advanced cardiac surgery in this country by using this principle. In dogs, they found that flow rates of 30 to 45 ml., as provided by cross circulation or some type of artificial heart-lung apparatus, were more suitable than the "azygos flow" rates of 10 to 18 ml. per kilogram per minute. Their successful experience with more than 110 patients has established the principle and the procedure as being clinically valid.

The possibility of using a small-flow rate revived the old idea of oxygenating blood in an apparatus using membranes. The advantages are obvious: there are no air bubbles, the possibility of air embolism is excluded; blood is not exposed to foam or screens or metal, so that potential sources of fibrin formation are eliminated.

During the earliest experience with the rotating type of artificial kidney in human beings, Kolff and Berk[8] observed that blue blood which entered the machine would become red during its course through the dialyzing tubing. Brubaker and Kammermeyer[9] compared the gas permeabilities of various membranes and found that polyethylene is permeable to both oxygen and CO_2. Clowes and associates[10] showed that the oxygenation of blood through a membrane of polyethylene of 1-mil thickness is much better than that through a membrane of 1.5-mil thickness. Kolff and Balzer[11] demonstrated a disposable artificial lung, later described in detail,[12] at the first meeting of the American Society for Artificial Internal Organs in 1955. It is based on the principle of oxygenation through a polyethylene membrane. One lung unit will oxygenate

From the Departments of Thoracic Surgery and Cardiovascular Disease and the Division of Research, The Cleveland Clinic Foundation and The Frank E. Bunts Educational Institute, Cleveland, Ohio.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

75 ml. of blood per minute; this, at a flow rate of 35 ml. per kilogram of body weight per minute, corresponds to the requirements of a 2-Kg. dog. By placing more than one unit in parallel, we can adapt the apparatus to dogs (or to children) weighing from 2 to 21 Kg. (4 to 47 pounds). During use, each lung unit holds 500 ml. of blood. Recent refinements in manufacture have reduced the amount of blood necessary to fill each unit to 270 ml.

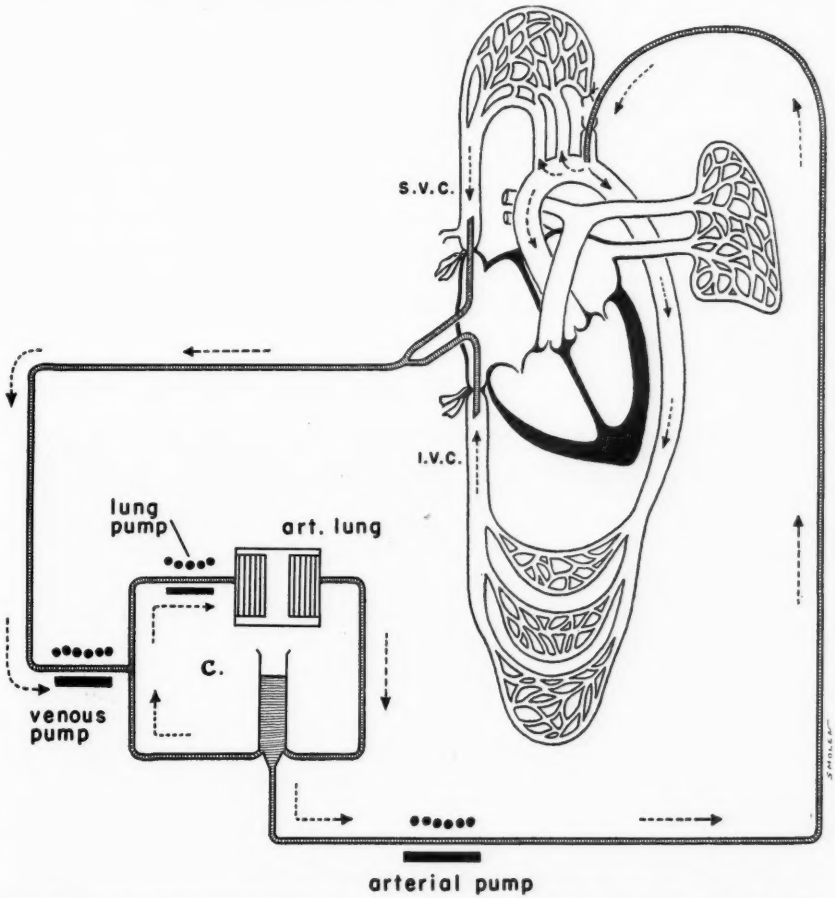


Fig. 1.—Diagram showing general principles of artificial maintenance of circulation. The blood is sucked out through two cannulae from the venae cavae. It is oxygenated and is pumped back into a branch of the aorta, in this case the left subclavian artery. The flow in the proximal part of the aorta is reversed and the coronary arteries having their openings above the aortic valve are provided with blood by the machine. When ligatures are tied around the roots of the venae cavae and the azygos vein, no blood will enter the heart, except that coming from the coronary sinus and the thebesian veins.

DESCRIPTION OF APPARATUS

The Artificial Lung.—After trying out various sizes, we selected the following type of polyethylene lung: 7-meter long strips of plastic-coated Fiberglas screen envelope two polyethylene tubes (Fig. 2). The polyethylene tubing has

a lay-flat diameter of 2 inches and its wall-thickness is 1/1000 of an inch (1 mil). The two tubes have an oxygenating area of 14,000 sq. cm. On each side of the tubing are spacers to allow some distention of the tubing when the blood flows through it. The 7-meter long strips are wound around tin cans

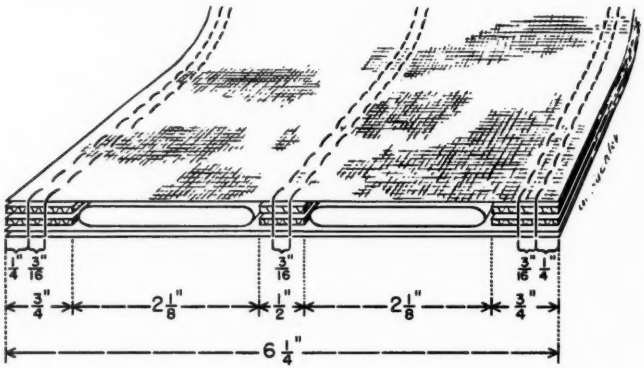


Fig. 2.—Cross section of membrane arrangement of the artificial lung. There are three layers of Fiberglas window screen, two tubes of polyethylene, and three pairs of spacers (to allow space for the tubes to become distended with blood). (Cross section through one coil of lung.)

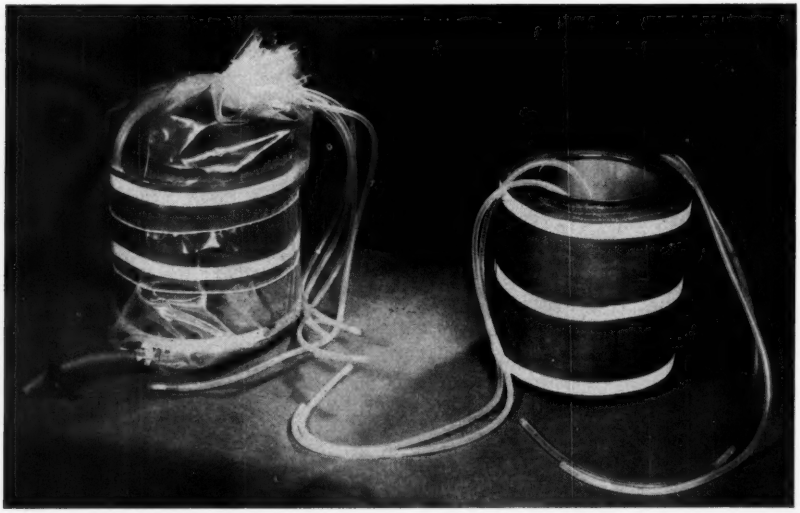


Fig. 3.—Artificial lung (right) and artificial lung in a plastic bag with tube for oxygen inlet at the bottom.

(10 cm. in diameter) and are provided with inlet and outlet tubing. The completed coil (Fig. 3) is placed in an ordinary transparent plastic bag, such as that used for vegetables. Warm (40° C.) oxygen is blown into the bottom part of the artificial lungs at a rate of 30 L. per minute (for eight lungs). A string

is tied around the top of the bag, just tightly enough so that oxygen flow will distend the bag, but loosely enough so that CO_2 and excess oxygen may escape through the top. The lungs are prefabricated and sterilized with ethylene oxide by Baxter Laboratories* and can be kept sterile until needed. Since the lung units are contained in transparent plastic bags, a blood leak can be seen. The lungs are pretested at the factory, and in our experience only one in approximately 160 units had to be replaced because of a leak.

The Pumps.—We use commercially available finger pumps (Sigmamotor pumps†). The variable-reduction transmissions in these pumps have been provided with dials for calibration.

The Blood Circuit.—In order to maintain a constant volume of blood in the oxygenator system we have adopted the third pump, as did Miller, Gibbon, and Gibbon.[13]

The center section of Fig. 4 outlines the lung circuit. The first step is to recirculate blood through this circuit at a constant rate. The lung pump is set to provide a flow slightly in excess of the maximal flow planned for the experiment. Since blood flow through the lungs, resistance in them, and the volume of blood that accumulates in them are stable, the blood in the collecting manifold assumes a constant level. Polyethylene is permeable to oxygen and CO_2 but is almost impermeable to water, so that there is no appreciable loss through evaporation. Changes in volume of as little as 20 ml. can be detected.

To establish an artificial circulation, the arterial pump is set at a predetermined rate (usually 35 ml. per kilogram of body weight per minute) and the venous pump is adjusted so that rates of inflow and outflow are identical, as judged from the level in the collecting manifold. Since the volume of blood in the manifold and burette is large, accidental sudden reduction of inflow does not immediately deplete blood from the machine or result in air embolism. When reduction of inflow does occur, it usually indicates that the dog has lost too much blood, so that caval flow is inadequate. When this is the case, the dog is transfused from the transfusion burette. Inadequate caval flow or obstruction of venous catheters may be recognized from an excessive negative pressure in the manometer attached to the bubble-catcher in the venous line.

Blood Used.—Blood is drawn into siliconized blood-transfusion bottles‡ containing 12 mg. of heparin in 30 ml. of diluent consisting of glucose, 2.5 per cent, and sodium chloride 0.45 per cent in water. Each bottle receives 500 ml. of blood. Usually the blood is collected by puncture of the femoral artery.

It is unnecessary to fill the machine with saline solution prior to use. The equipment is assembled dry and it is directly primed with blood. This avoids undesirable dilution of the donor blood with saline solution.

The blood lost during operation is collected in a measuring cylinder that is coated with antifoam A so that the volume can be measured accurately without being obscured by foam. An equivalent volume of blood is replaced and an additional 15 ml. per kilogram of body weight is transfused during each run.

*Baxter Laboratories, Morton Grove, Illinois.
†Sigmamotor, Inc., Middleport, New York.
‡Provided through the courtesy of Baxter Laboratories.

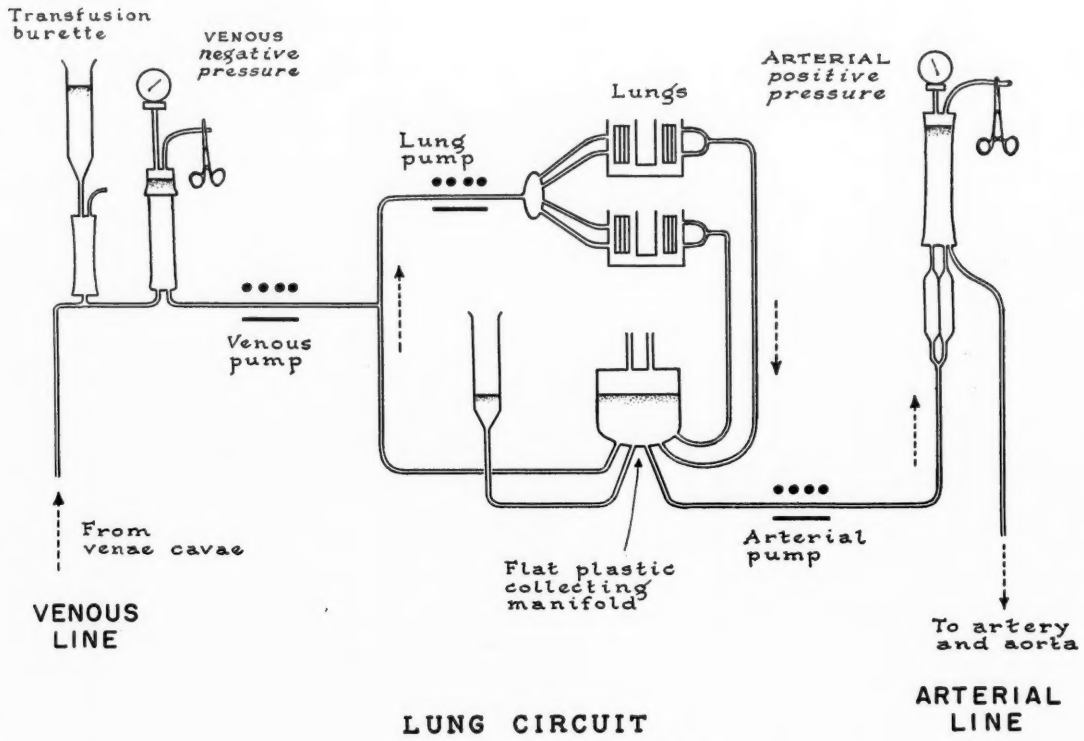


Fig. 4.—*For legend see opposite page.*

TECHNIQUE

In the first series of experiments a total of 140 dog operations were performed. The animals were prepared for surgery by antibiotics (penicillin 400,000 units, and streptomycin mg. 0.5) the day before. Five to 15 mg. of morphine was given preoperatively; endotracheal anesthesia was employed routinely using Pentothal sodium (1 per cent), succinylcholine supplement, and oxygen.

In the early experiments, testing of the oxygenator was the main purpose, and cannulations were performed from the neck. Later, to prepare for clinical use, intrathoracic cannulations were performed and every effort was made to simulate a human operation. The operative technique has been described by Lillehei and co-workers. The experimental operations were carried out in graded sequence (Table I). At first only caval occlusion was employed to test the

TABLE I. RESULTS OF EXPERIMENTS WITH ARTIFICIAL HEART-LUNG MACHINE

LIGATURE OF VENAE CAVAE	RIGHT AURICLE OPENED	RIGHT VENTRICLE OPENED	INTERATRIAL SEPTAL DEFECT MADE AND CLOSED	INTERVENTRICULAR SEPTAL DEFECT MADE AND CLOSED
+	−	+	−	−
−*	−	−	−	+
+	+	−	−	+
+	+	−	−	+
+	+	−	+	+
+	+	+	−	−
	+	−*	−	+
	+	+	−	
	+	+	+	
			+	
			+	
			−	

Each + or − represents one dog.
+ = Dog survived and recovered completely.
− = Dog died within two days after the operation.
−* = Dog died more than one week after the operation.

oxygenator's ability to sustain the animal. The individual heart chambers were opened and closed; finally septal defects were created and closed. With each step there was an initial toll until experience and analysis of mistakes brought improvement.

RESULTS

Hemolysis.—Dog blood hemolyzes readily and hemolysis depends largely on the method of drawing blood. Good control of hemolysis was achieved by draw-

Fig. 4.—Artificial heart-lung circuit. Blood coming from the venae cavae passes a bubble catcher with a negative-pressure manometer that indicates the degree of suction. The venous pump delivers the blood into the lung circuit. The arterial pump at right, pumps the oxygenated blood out of the circuit through two filters, and a bubble catcher with a positive-pressure manometer. This manometer indicates the animal's blood pressure when the pump is not running. It will indicate the sum of the animal's blood pressure, plus the pressure necessary to overcome the resistance in the arterial lines and cannulae while the pump is running. In the center of the figure is the lung circuit. The lung pump is set at a rate slightly higher than the highest rate at which the arterial pump will work in the particular experiment. The speed of the lung pump is not changed; with both venous and arterial pumps not running, an equilibrium is established and the blood in the collecting manifold stays at the same level. When the venous and arterial pumps are started and the level is maintained, input and output of the machine are exactly alike.

ing blood into siliconized bottles* and by avoiding the formation of foam. Often 4 dogs were operated upon on the same day with the same blood in the machine; plasma hemoglobin in the machine taken at the beginning and end of the day showed an average increase of less than 20 mg. per hundred milliliters. Hemoglobinuria was never observed.

Oxygenation.—Determinations were initially made by the Van Slyke method; later the reflex oximeter of Brinkman† was used. One lung unit could oxygenate 75 ml. of blood per minute. Although oxygen saturation of venous blood is low when the small-flow principle is used, the oxygen saturation of the arterial blood still was over 90 per cent.

Acidosis (pH and CO_2).—The dogs were hyperventilated prior to the run on the heart-lung machine. CO_2 is effectively removed from circulating blood when recirculated in the oxygenator; although the CO_2 is reduced during recirculation of blood the pH is only slightly altered.

Metabolic acidosis must be expected during extracorporeal maintenance of circulation especially when the small-flow principle is followed. With sodium bicarbonate this acidosis can be corrected. A continuous drip of sodium bicarbonate (4.5 meq. per kilogram body weight made up to 100 ml. with 5 per cent fructose in water) is routinely administered during the run. A second dose is given during the first three hours postoperatively.

Temperature.—The oxygen going into the artificial lungs was heated to 40° C. but no other heating of the blood in the machine was provided. Consequently the dogs showed a fall in body temperature down to 34° C. during the run. This was corrected with a heating pad.

Disturbances in Clotting Mechanism.—The tendency of the animal to bleed has created difficulties for numerous investigators in this field. We also have lost a number of dogs from oozing or diffuse hemorrhage. In our recent experiments this complication has become rare. Heparin has been given: 0.8 mg. per kilogram of body weight to the dogs and 12 mg. per 500 ml. of blood. Heparin was neutralized with protamine sulfate (Upjohn), 25 mg. for small and 50 mg. for large dogs. This was followed by a continuous intravenous infusion of the same amount of protamine sulfate to prevent "heparin rebound."

Heparin Rebound.—This is a treacherous hemorrhagic phenomenon. When heparin is neutralized by protamine sulfate, the clotting time becomes normal in a matter of minutes. However, protamine sulfate seems to be eliminated from the blood stream before heparin is, thus leaving the heparin uncovered, as demonstrated by protamine titration.[14]

Thrombocytes.—Usually there is a transient fall in platelet counts, but it did not always occur. Within one hour the platelets were back to normal. The excellent clot retraction after administration of protamine sulfate also indicated normal platelet function.[12]

Prothrombin Times.—During treatment with the artificial heart-lung, prothrombin times changed no more than might be expected from hemodilution.[12]

*Baxter Laboratories, Morton Grove, Illinois.
†Manufactured by Kipp in Delft, Holland.

This excludes damage to the early phases of the clotting mechanism in the two experiments studied.

Bleeding Time.—Stabbing with a hemolet into the undersurface of the dog's tongue at the end of the experiment and after administration of protamine sulfate did not reveal a prolongation of the bleeding time in any of the dogs in which it was tested.

The general conclusion in regard to clotting mechanism with this type of artificial heart-lung is that when heparin is adequately neutralized with protamine sulfate, only transient changes in the clotting mechanism occur. Within 15 minutes, the changes revert to normal. However, the use of old blood, large amounts of dextran, or failure to clean parts of the machine affects the clotting mechanism disastrously.

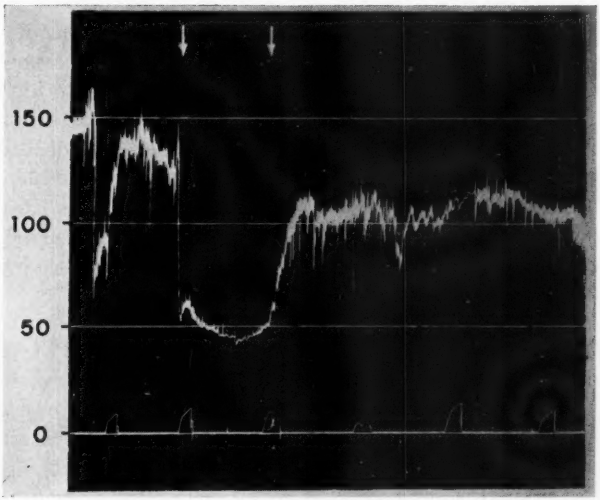


Fig. 5.—Experiment 55. Arterial blood pressure is indicated in mm. Hg. Time is indicated at the bottom in 10-minute intervals. At the first arrow, the artificial heart-lung is started and ties are put around the venae cavae. There is a sharp drop in arterial pressure and during the following minutes the right ventricle is opened. It is closed, and at the second arrow the ligatures are removed from the venae cavae. Blood pressure rises to about 100 mm. Hg within a few minutes.

Arterial Pressure.—Arterial pressure ranged from 25 to 50 mm. Hg during occlusion of the venae cavae and extracorporeal circulation, at 35 ml. per kilogram per minute; it returned to 100 mm. Hg within 5 minutes after release of the venae cavae in most successful experiments (Fig. 5).

Venous Blood Pressure.—The continuous observation of the venous blood pressure during the postoperative course has been very helpful in some cases when trouble arose. When both the venous pressure and the arterial pressure are low, the dogs should most likely be tranfused. When the venous pressure is high while the arterial pressure is low, the cause of trouble should be other than loss of blood. It may be that the closure of the pericardium over the distended heart is too tight or it may be failure of the right ventricle.

"Second Run."—Thirteen dogs had low arterial blood pressure after the experiments, which evidently was due to cardiac failure. Extensive cutting into the interventricular septum probably was the cause. It has been possible to bring them into better condition by reconnecting them to the artificial heart-lung machine, leaving caval flow intact and using either the original cannulae or peripheral cannulation. In some dogs the artificial heart-lung machine was restarted two or three times. One dog was reconnected to the machine five hours after completion of the first experiment. It recovered.

Ventricular Fibrillation.—Ventricular fibrillation has occurred only three times in 125 experiments. Cardiac massage was not necessary during artificial maintenance of the circulation. The heart of one dog (No. 61) fibrillated after it had been closed and the machine had been stopped. The machine was started again for 8 minutes before a defibrillator was available. The heart of a second dog (No. 106) began to fibrillate 30 minutes after completion of the cardiac operation. The cannulae still were in place and he was reconnected to the machine. The heart of the third dog (No. 113) started to fibrillate when the chest was opened. The dog quickly was connected to the artificial heart-lung machine. Ventriculotomy was performed and the heart was defibrillated. All three hearts could be defibrillated, and normal cardiac action and blood pressure were restored, although later we lost the dogs. The last dog died two days after the operation from atelectasis. Fibrillation also has occurred, as will be discussed later, in dogs treated with elective potassium arrest; they recovered.

SUMMARY

Artificial heart-lung machines operate on the principle of taking blood from the occluded venae cavae, oxygenating it, and returning it to the aorta, so that the heart is by-passed. The artificial lungs described here oxygenate blood while it flows through polyethylene tubing. The lung unit discussed has an oxygenating area of 14,000 sq. cm., will oxygenate 75 ml. of blood per minute, and holds 500 ml. of blood. A recent refinement in manufacturing reduced the amount of blood needed to "prime" a unit to 270 ml. The lung units are disposable and simple enough to be mass-produced. As many as ten units may be used in parallel.

Experience in about 140 experiments in dogs is reviewed. Anesthesia was light and blood loss was fully replaced. Oxygenation was more than 90 per cent, even when the venous inflow was highly unsaturated. Hemolysis was negligible. Metabolic acidosis was countered, first by hyperventilation, and secondly by operative and postoperative infusions of sodium bicarbonate (4.5 meq. per kilogram of body weight each). Serum sodium increased within the normal range and serum potassium was not changed.

Bleeding problems were largely overcome. Transient disturbances of clotting mechanisms during the run, quickly reverted to normal. "Heparin rebound" was recognized by protamine titration. It was corrected, and later prevented by repeated doses or infusion of protamine sulfate.

REFERENCES

1. Andreasen, A. T., and Watson, F.: Experimental Cardiovascular Surgery, Brit. J. Surg. **39:** 548, 1952.
2. Andreasen, A. T., and Watson, F.: Experimental Cardiovascular Surgery; Discussion of Results So Far Obtained and Report on Experiments Concerning Donor Circulation, Brit. J. Surg. **41:** 195, 1953.
3. Lillehei, C. W.: Controlled Cross Circulation for Direct-Vision Intracardiac Surgery; Correction of Ventricular Septal Defects, Atrioventricularis Communis, and Tetralogy of Fallot, Postgrad, Med. **17:** 388, 1955.
4. Lillehei, C. W., Cohen, Morley, Warden, H. E., Read, R. C., Aust, J. B., DeWall, R. A., and Varco, R. L.: Direct Vision Intracardiac Surgical Correction of Tetralogy of Fallot, Pentalogy of Fallot, and Pulmonary Atresia Defects; Report of First Ten Cases, Ann. Surg. **142:** 418, 1955.
5. Lillehei, C. W., Cohen, Morley, Warden, H. E., and Varco, R. L.: Direct-Vision Intracardiac Correction of Congenital Anomalies by Controlled Cross Circulation; Results in Thirty-Two Patients With Ventricular Septal Defects, Tetralogy of Fallot, and Atrioventricularis Communis Defects, Surgery **38:** 11, 1955.
6. Lillehei, C. W., Cohen, Morley, Warden, H. E., Ziegler, N. R., and Varco, R. L.: Results of Direct Vision Closure of Ventricular Septal Defects in Eight Patients by Means of Controlled Cross Circulation, Surg., Gynec. & Obst. **101:** 446, 1955.
7. Warden, H. E., Cohen, Morley, DeWall, R. A., Schultz, E. A., Buckley, J. J., Read, R. C., and Lillehei, C. W.: Experimental Closure of Interventricular Septal Defects and Further Physiologic Studies on Controlled Cross Circulation, Surg. Forum, Clin. Congress Am. Coll. Surgeons (1954), Philadelphia, 1955, W. B. Saunders Company, pp. 22-28.
8. Kolff, W. J., and Berk, H. T. J.: Artificial Kidney: Dialyser With Great Area, Acta med. scandinav. **117:** 121, 1944.
9. Brubaker, D. W., and Kammermeyer, Karl: Separation of Gases by Plastic Membranes, Permeation Rates and Extent of Separation, Indust. & Chem. Eng. Chemistry **46:** 733, 1954.
10. Clowes, G. H. A., Hopkins, A. L., and Kolobow, T.: Oxygen Diffusion Through Plastic Films, Transactions of the American Society for Artificial Internal Organs (1955) **1:** 23, 1956. (Published by the Society: Dr. P. Salisbury, 4751 Fountain Ave., Los Angeles 29, Calif.)
11. Kolff, W. J., and Balzer, R. R.: Artificial Coil Lung. Transactions of the American Society for Artificial Internal Organs (1955) **1:** 39, 1956. (Published by the Society: Dr. P. Salisbury, 4751 Fountain Ave., Los Angeles 29, Calif.)
12. Kolff, W. J., Effler, D. B., Groves, L. J., Peereboom, G., and Moraca, P. P.: Disposable Membrane Oxygenator (Heart-Lung Machine) and Its Use in Experimental Surgery, Cleveland Clin. Quart. **23:** 69, 1956.
13. Miller, B. J., Gibbon, J. H., Jr., and Gibbon, M. H.: Recent Advances in Development of Mechanical Heart and Lung Apparatus, Ann. Surg. **134:** 694, 1951.
14. Kolff, W. J., Effler, D. B., Groves, L. K., Peereboom, G., Aoyama, S., and Sones, F. M., Jr.: Elective Cardiac Arrest by Melrose Technic: Potassium Asystole for Experimental Cardiac Surgery, Cleveland Clin. Quart. **23:** 98, 1956.

AN ARTIFICIAL LUNG DEPENDENT UPON DIFFUSION OF OXYGEN AND CARBON DIOXIDE THROUGH PLASTIC MEMBRANES

GEORGE H. A. CLOWES, JR., M.D., AMOS L. HOPKINS, PH.D. (BY INVITATION), AND WILLIAM E. NEVILLE, M.D. (BY INVITATION)
CLEVELAND, OHIO

A PRACTICAL blood oxygenator dependent upon the diffusion of gases through plastic membranes has been constructed and tested. It is the purpose of this paper not only to present this apparatus but to outline the physiologic concepts which entered into its development.

Denaturation of proteins is known to occur at a gas fluid interface,[1] and several years ago we demonstrated the formation of fibrin emboli by a bubbling type of oxygenator.[2] This resulted in brain damage and a high mortality in dogs perfused for more than one-half hour. Despite the outstanding successes of Lillehei and his co-workers using a bubbling device[3] and by Kirklin and his associates[4] using the Gibbon filming oxygenator, it was believed necessary to explore the possibilities of completely protecting blood from gaseous oxygen as is done in the naturally occurring gill and lung. Kolff and Blazer,[5] employing a modification of the Inouye artificial kidney,[6] have approached the problem from a similar viewpoint.

The experiments to be presented were divided into two parts. The first, to determine the permeability to oxygen and carbon dioxide of the available thin plastic films; a variety of these were tested in a diffusion chamber. The second dealt with the development and study of models to employ ethylcellulose and polyethylene membranes. From these studies have come an understanding of certain principles which govern the use of membranes for the oxygenation of flowing blood.

PERMEABILITY OF MEMBRANES TO BLOOD GASES

The rate of diffusion of oxygen and carbon dioxide through a variety of thin plastic membranes was measured in an apparatus containing a known quantity of venous blood on one side of the membrane and flowing oxygen on the other. Temperature was maintained at approximately 33° C., and the blood was kept well mixed by constant motion. Samples were taken every ten minutes for Van Slyke analysis,[7] or for determination of oxygen saturation by the Wood oximeter.[8] The rate of oxygen diffusion through the various membranes was compared by the formula:

$$\text{c.c. } O_2 \text{ diffusion/sq. m. surface area/min.} = \frac{\triangle O_2 \text{ content (vols. \%)} \times \text{volume blood} \times 100}{\text{surface area membrane (sq. cm.)} \times \triangle T \text{ (min.)}}.$$

From the Department of Surgery, Western Reserve University School of Medicine, Cleveland City Hospital, Cleveland, Ohio.

This project was in part supported from a grant from the Cleveland Area Heart Society.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

To assure the greatest attainable value for each membrane, measurements of $\triangle O_2$ content were made during the steep part of each dissociation curve.

In Table I are given data indicating that of the available films tested, ethylcellulose, one mil in thickness,* is superior to other materials in its oxygen permeability. Polyethylene† and pure cellophane,‡ next in order of efficiency, compare favorably in certain respects with ethylcellulose. Both ethylcellulose and polyethylene do not permit passage of electrolytes, although ethylcellulose permits water to evaporate at a very slow rate through itself. Cellophane rapidly becomes coated with a dried deposit if fluid is not used on both sides. This is a serious disadvantage for use in oxygenation in that the membrane becomes increasingly less permeable to gases. Also, considerable quantities of fluid may be lost by evaporation through this film. Carbon dioxide was found to diffuse out of blood through all three films at a rate proportional to the oxygen uptake.

TABLE I. RATE OF OXYGEN DIFFUSION THROUGH PLASTIC MEMBRANES INTO VENOUS BLOOD

MEMBRANE	THICKNESS (INCHES)	C.C. O_2/SQ. METER/MIN.	
		VARIATION	MEAN
Ethylcellulose	.001	7.6-13.1	11.4
	.003	3.7- 5.2	4.3
Polyethylene	.0008	6.2- 8.9	8.2
	.001	6.3- 8.1	7.6
Cellophane	.001	7.0- 7.7	7.4
	.003	5.1- 6.9	6.0
Polyvinylchloride	.005	1.1- 1.6	1.4
	.010	0.6- 0.72	0.7
Polystyrene	.001	2.0- 2.8	2.5
Mylar	.0002	0.4- 1.0	0.5
Chlorinated rubber	.0004	0.1- 0.6	0.4

Whereas, polyethylene is soft, pliable, and can be heat sealed, ethylcellulose is brittle, fairly easily torn, and cannot be sealed. The former is available either as tubes or sheets, but the latter, being a cast membrane, is obtainable at present only in sheet form. Both membranes of one-mil thickness have tiny pinhole perforations, but there are many more at present in a given surface area of ethylcellulose than of polyethylene.

DEVELOPMENT OF AN OXYGENATOR EMPLOYING ETHYLCELLULOSE MEMBRANES

A variety of small models were constructed to test the possibility of using ethylcellulose and polyethylene membranes to oxygenate flowing blood.

In general, two methods for support of membranes were tried. The first depended upon flowing blood along a screen with ethylcellulose membranes on either side held in apposition by oxygen pressure outside. The second depended upon grooved surfaces to hold the membranes together. Blood flowed between

*Made available through the kindness of the Plastics Technical Service, The Dow Chemical Company, Midland, Mich.

†Kindly supplied by the du Pont Company, Wilmington, Del., and by the Dobeckmun Company, Cleveland, Ohio.

‡Kindly supplied by the Visking Corporation, Chicago, Ill.

the membranes, while oxygen flowed in the grooves outside. Since sheet membrane was used, it was necessary to support all four edges by rubber gaskets to prevent leakage.

The best of the latter type was developed into a multilayered apparatus with 6 square meters of surface area capable of supporting the whole circulation of small dogs up to two hours with complete recovery.

METHODS AND PROCEDURES

To evaluate the efficiency as well as the damage to blood done by each model of the oxygenator, the following general procedure has been followed. Venous blood from a heparinized dog was pumped into the apparatus between the layers of membrane and made to flow at a known rate. The oxygenated blood coming from the apparatus was returned under pressure to the carotid artery in such a fashion that the brain was perfused. This matter was established by the injection of radiopaque dye into the blood as it was perfused into the carotid artery. An x-ray made approximately five seconds later revealed the whole of the cerebral circulation to be outlined. These procedures were carried on for a minimum of one hour and usually longer. Sigmamotor pumps were used for convenience.

During each experiment the following observations were made: (1) oxygen and carbon dioxide contents of the venous and arterial blood as it entered and left the apparatus were determined by the method of Van Slyke; (2) blood flow was accurately determined in cubic centimeter per minute by timed collection of outflow in a reservoir, thus, it became possible to calculate exactly how much oxygen was passing into the venous blood per minute per square meter of surface area; (3) pressure of blood entering the apparatus was measured by a mercury manometer attached to the inflow line giving an index of resistance; (4) the electro-encephalogram was recorded on a Grass oscillograph during the perfusion; (5) clinical observations were made on the dog to determine evidence of brain damage.

RESULTS

Although considerable efficiency in oxygenation was obtained by causing blood to flow down a screen between layers of membrane held in close apposition by exterior oxygen pressure, imperfections in the membrane resulted in oxygen being forced into the film of blood. This caused bubble formation and immediately defeated the object of the membrane oxygenator.

Attention was devoted entirely, thereafter, to the development of oxygenators in which the oxygen pressure was maintained at a lower pressure outside the membrane than that of the blood inside. A variety of techniques for using wire screens or grooved surfaces for outside support of the membranes were tried. Screens tended to tear the membranes. Hard rubber ridges with 1/8-inch grooves between, when placed at 60 degrees or at 90 degrees to each other on the two sides of the membranes, resulted in a type of point suspension. If these were firmly held together, enough stretch took place in the membranes to allow the blood to flow between them. Oxygen was made to flow in the grooves outside the membranes.

Resistance within the oxygenator was found to be proportional to the distance blood was made to flow between the membranes and inversely proportional to the width of the film as it flowed across the oxygenating unit. To reduce the volume of blood trapped within each unit to a minimum, it was necessary to maintain as thin a film as possible with distributing channels down the sides of each unit of as small a cross section area as possible. It will be seen by the diagram in Fig. 1 that the side distributing channels are made by the bulging of the two membranes into the space between the rubber gaskets and the hard rubber diagonal ridges. Without increasing resistance materially, it was found that the flowing blood volume of each unit could be reduced to between 40 and 60 c.c.

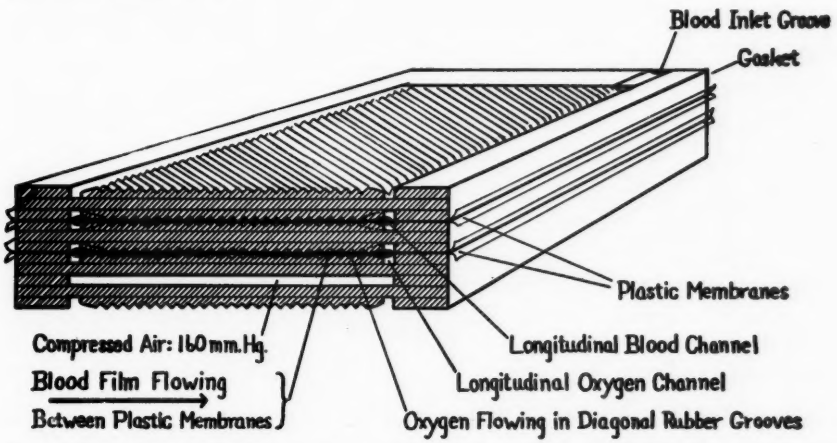


Fig. 1.—A cross section diagram of the multiple-unit membrane oxygenator showing the course of blood and oxygen flow.

Ethylcellulose, one mil thick, in single units introduced on the average 8.6 c.c. of oxygen per square meter of surface area per minute into blood flowing at 100 c.c. per minute. This compares with the theoretical value of 11.4 obtained from the data in Table I. Through polyethylene (0.8 mil), oxygen diffused at a rate of 5 c.c. per sq. M. per minute which is approximately the same order of efficiency. If the flow was reduced to 50 c.c. per unit, the atrioventricular (A-V) difference of blood oxygen content did not double, and oxygen was transmitted less efficiently. In all probability this was due to a reduction of pumping pressure to about 85 mm. Hg which failed to open all the channels between the grooves.

Blood from single units being tested was pumped into the carotid arteries of dogs at a rate of 100 c.c. per minute for periods of one to four hours. There was no evidence of brain damage in these animals as indicated by a depression of electroencephalogram potential. They recovered without incident.

A MULTIPLE-UNIT MEMBRANE OXYGENATOR

A multiunit apparatus is illustrated in Fig. 3. A variable number of units were employed depending upon the surface area desired. The separators

which contain the grooved surfaces for support of the membranes are illustrated in Fig. 2. Each of these is constructed of hard rubber flooring material with 1/8-inch grooves between the ridges which are set at a 60 degree angle to each other and at a 30 degree angle to the crosswise direction of blood flow. This is mounted on 1/8-inch gum rubber and is surrounded by a 1/8-inch gum rubber gasket. The actual oxygenating surface upon which the membrane lies measures 10 by 42 inches. To avoid tearing the membranes, the grooved material is slightly beveled along the sides.

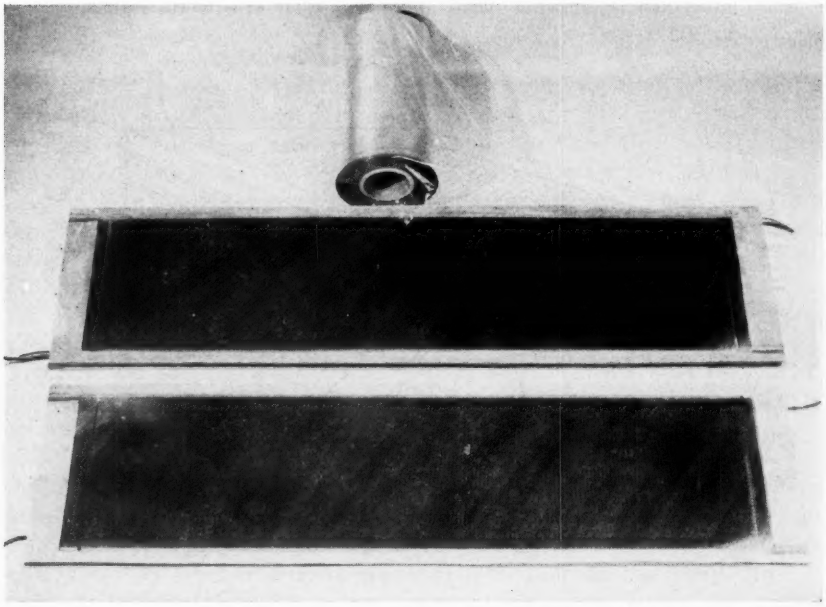


Fig. 2.—Illustration of the grooved separators for support of the membranes. The upper separator is inflatable. The flexible rubber tubes at the ends are for the introduction and exit of oxygen. Shown at the top is a roll of ethylcellulose, one mil thick.

The diagram in Fig. 1 illustrates the way in which the apparatus functions. Through a manifold, venous blood enters each unit at one corner under pressure. A connecting tube lying between the membranes held firmly in the blood inlet groove permits the blood to enter the space between the membranes. Distending the membranes slightly in the space between the gasket and the grooves, the blood flows down the side. Being forced across the oxygenating area in a thin film, it collects on the opposite side in a similar longitudinal channel down which it flows to an outlet tube. This lies in a groove in the diagonally opposite corner to the inlet tube. The oxygenated blood is collected by a manifold system to be pumped back into the arterial circuit.

Pressure of the grooved surfaces against each other for support of the paired membranes is maintained by every fourth separator being inflated to a pressure of 160 mm. Hg. This is illustrated diagrammatically at the bottom

of Fig. 1. In Fig. 3, three tubes may be seen connected to these units at the middle of the near end. Stacked up units are held between heavy pieces of plastic at top and bottom. The whole apparatus being firmly clamped together with large "C" clamps. Oxygen enters each unit through a flexible rubber tube and flows down the longitudinal space between the gaskets and the grooves. It then passes across through the grooves to the opposite longitudinal space to exit at the far corner. At the near corner of Fig. 3 is shown the oxygen distributing manifold connected to the oxygen inlet tubes. All exterior blood connections are made of plastic or gum rubber. Glass is almost entirely eliminated.

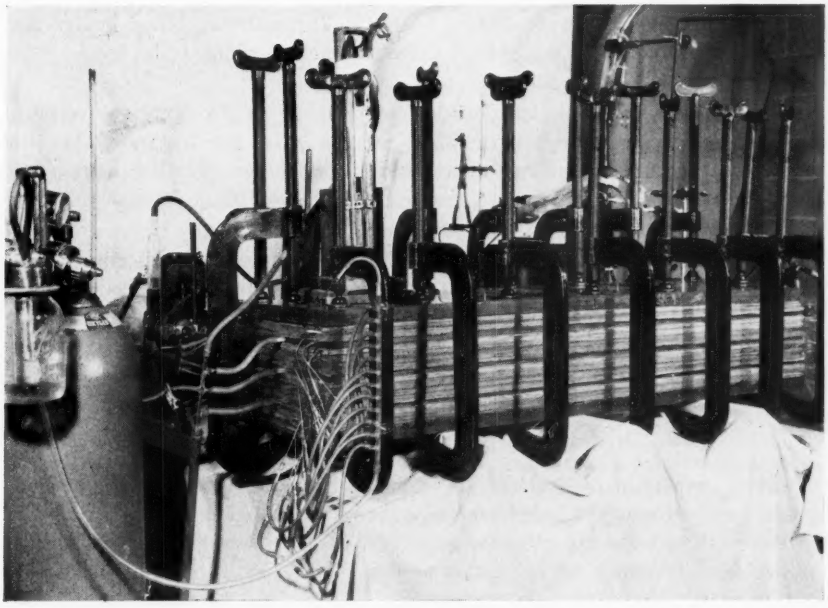


Fig. 3.—The 12-unit membrane oxygenator in operation as seen from the end into which venous blood is being pumped.

Using this device, it has been found that the greatest efficiency in oxygenation is produced if approximately 100 c.c. per minute of blood is pumped through each unit. This requires a pressure of approximately 120 mm. Hg. Data on oxygen transmission to blood by the multiple-unit system are given in Table II.

TABLE II. RATE OF OXYGEN DIFFUSION INTO BLOOD FLOWING THROUGH OXYGENATOR

MEMBRANE	INCHES	RATE OF FLOW (C.C./SQ. M./MIN.)	BLOOD TRAPPED (C.C./SQ. M./AREA)	MEAN BLOOD O_2 UPTAKE		
				A-V DIFF.	C.C./SQ. M./MIN.	EFFICIENCY
Ethylcellulose	.001	200	80-120	4.1	8.4	74%
		100	70-100	6.2	6.2	54%
Polyethylene	.0008	200	120-160	2.7	5.4	71%

Note: Each unit of oxygenator has 0.5 square meter surface area.

Reduced flow rates resulted in less efficient oxygenation. Flow rates greater than 100 c.c. per minute through each unit caused bulging of the membranes and increased blood trapping within the apparatus. To maintain the optimum flow through the oxygenator a recirculation shunt was introduced to permit lower flows to the animal. Thus, with a 12-unit system functioning well, it was possible to pump 300 c.c. of blood per minute with an A-V difference of 16 volumes per cent, 600 c.c. with an A-V difference of 8 volumes per cent, or 1,200 c.c. with an A-V difference of 4 volumes per cent.

Ten dogs were subjected to partial perfusion through the carotid artery without brain damage. When total perfusions were undertaken with diversion of all circulation from the heart and lungs, it was found that cooling rapidly took place to levels between 28° and 32° C. Thereafter, a blood heater was incorporated into the arterial blood delivery line by which body temperature was easily controlled.

A consecutive series of 10 dogs weighing up to 10 Kg. were subjected to total perfusions for periods over thirty minutes. In two instances this was carried on successfully for two hours, and in two others, for one hour. One dog died ten hours postoperatively of continued bleeding. In none of these was there evidence of cerebral damage.

Ethylcellulose, one mil thick, was used for the experiments described above. The chief problem encountered in this series was leakage of blood through very small holes in the membranes into the oxygen grooves rendering the apparatus less effective as time of perfusion progressed. Another two perfusions were carried out using polyethylene film 0.8 mil in thickness. Leakage with this material was slight but oxygen transmission was less satisfactory.

DISCUSSION

These experiments demonstrate that it is possible to oxygenate blood satisfactorily through thin plastic membranes provided that the surface is large enough to transmit adequate quantities of oxygen to sustain life without undue blood trapping or resistance to flow. Data in Table I indicate that definite limitations of oxygen transmission are imposed by the characteristics of the membrane used. Efficient use of the membrane surfaces was obtained by causing blood to flow in a thin film between them without pooling, stasis, or channelling. This required even support of the membranes from the outside. Resistance was reduced by a short but effective exposure of the blood to the membrane area as is done in the capillaries of the lung. To avoid undue trapping of blood in the apparatus, distribution to the film areas was accomplished in the smallest channels consistent with reasonably low resistance to flow. Finally, oxygen was made to flow freely over the outside surface of the membrane to avoid channelling or stoppage of oxygen flow. This corresponds to the mixing problems encountered in the lung.

The lack of brain injury in animals, perfused so that the majority of the blood from the oxygenator was circulated through the cerebral vessels, suggests that embolus formation and other blood damage was minimal.

The multiple-unit system capable of expansion to furnish an adequate oxygen supply for a given organism has proved capable of sustaining life for prolonged periods when the heart and lungs are rendered inoperative. The fact that each unit can transmit 4 c.c. of oxygen per minute to flowing blood, yet only contains 40 to 50 c.c. of blood when in operation, makes it a reasonably practical piece of equipment for clinical use. It should be emphasized that this apparatus is presented not as a finished article but as a functioning oxygenator which illustrates the principles which govern the use of membranes in the artificial oxygenation of blood.

SUMMARY

1. Diffusion tests suggest that of the available thin plastic membranes, ethylcellulose permits the greatest passage of oxygen and carbon dioxide. Polyethylene is approximately three fifths as effective.

2. Efficient oxygenation of blood with membranes can be accomplished with a surface area adequate to transmit the necessary quantity of oxygen provided resistance to blood flow and trapping of blood are reduced to a minimum.

3. A multilayered system has been constructed capable of oxygenating blood adequately for support of the circulation of dogs when the heart and lung were not functioning. Nine of 10 dogs so treated survived.

The authors wish to express their appreciation to Mr. Howard Peacock for his interest and help in this project.

REFERENCES

1. Mirsky, A. E.: Sulfhydryl Groups in Films of Egg Albumin, J. Gen. Physiol. **24**: 725-33, 1940-1941.
2. Clowes, G. H. A., Jr., Neville, W. E., Hopkins, A. L., Anzola, J., and Simeone F. A.: Factors Contributing to Success or Failure in the Use of a Pump Oxygenator for Complete By-Pass of the Heart and Lung, Experimental and Clinical, Surgery **36**: 557-79, 1954.
3. Lillehei, C. W., DeWall, R. A., Read, R. C., Warden, H. E., and Varco, R. L.: Direct Vision Intracardiac Surgery in Man Using A Simple Disposable Artificial Oxygenator, Dis. Chest **29**: 1, 1956.
4. Kirklin, J. W., DuShane, J. W., Patrick, R. T., Donald, D. E., Hetzel, P. S., Harshbarger, H. G., and Wood, E. H.: Intracardiac Surgery With the Aid of a Mechanical Pump-Oxygenator, Proc. Staff Meet., Mayo Clin. **30**: 201, 1955.
5. Kolff, W. J., and Balzer, R.: The Artificial Coild Lung, Amer. Soc. Art. Int. Organs **1**: 39, 1955.
6. Inouye, W. Y.: Construction and Performance of Our Dialyzer, Amer. Soc. Art. Int. Organs **1**: 36, 1955.
7. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**: 523, 1942.
8. Wood, E. H., and Geraci, J. E.: Photoelectric Determination of Arterial Oxygen Saturation in Man, J. Lab. & Clin. Med. **34**: 387, 1949.

EXTRACORPOREAL CIRCULATION FOR OPEN HEART SURGERY

RUSSELL M. NELSON, M.D., PH.D. (BY INVITATION), HANS H. HECHT, M.D. (BY INVITATION), RICHARD W. HARDY, M.D. (BY INVITATION), DONALD G. MCQUARRIE, M.D. (BY INVITATION), AND JOE BURGE, M.D. (BY INVITATION)
SALT LAKE CITY, UTAH

THE initial studies by Gibbon in 1937[5, 6] concerning the possibility of extracorporeal perfusion for open heart surgery under direct vision have led to intensive investigations in many laboratories. Since the first application of this technique in human subjects by the Minnesota group in 1951,[3] this approach has become more widely adopted. The definition of the "azygos flow principle" (or perfusions of less than full cardiac output), by Cohen in 1954,[2] provided a factor which laid the foundation for controlled cross circulation, first successfully employed in human cardiac surgery by Lillehei and his associates in 1954.[11, 19] This method of perfusion demonstrated clearly that corrective open heart surgery was possible. Efforts were then accentuated to bypass the heart temporarily by completely artificial means, thereby obviating the need for a human donor. Perfusions were next accomplished by means of a reservoir of arterialized blood,[18] and oxygenation by means of a dog lung,[12] followed shortly by wider scale application of the Gibbon type machine.[4, 9, 10] Still the need was apparent for the development of a less complex apparatus capable of pumping and oxygenating the blood for the time necessary for the correction of intracardiac abnormalities. With this in mind, the technique to be described was developed.

Since this work was inaugurated, Lillehei has used the DeWall artificial lung with repeated success, again demonstrating the reality of satisfactory extracorporeal circulation to permit intracardiac surgery under direct vision.[14]

METHOD

A. *The Artificial Heart-Lung Apparatus.*—

1. The pump used is that developed for the cross circulation procedure of Lillehei.* It consists of a single explosion-proof electric motor (⅓ horsepower) which drives two finger pumps regulated by separate transmissions. By individual adjustment of vernier control, the flow rates of the two pumps can be balanced.[13] We have routinely employed Latex tubing, ½ inch I.D., to serve as the "ventricle" in the pumping chamber.

From the Departments of Surgery and Medicine, University of Utah College of Medicine, Salt Lake City, Utah.

Supported by grants from the University of Utah Alumni Development Fund, from the University of Utah Research Fund, the Ciba Pharmaceutical Company, and a cardiovascular training grant of the National Heart Institute (USPHS).

Read at the Thirty-sixth Annual Meeting of the American Association for Thoracic Surgery at Miami Beach, Fla., May 7-9, 1956.

*By Sigmamotor, Inc., Middleport, N. Y.

2. The oxygenator is depicted in Fig. 1. It consists of two concentric Lucite cylinders. The inner cylinder constitutes the foaming chamber and measures 1¼ inches I.D. by 14 inches in height. The outer chamber is 4¼ inches in diameter and 17 inches in height. Another antifoamed-screen rests below the top of the center column to reduce secondary splash effects. It is sloped on the bottom to provide for dependent drainage. The outer chamber

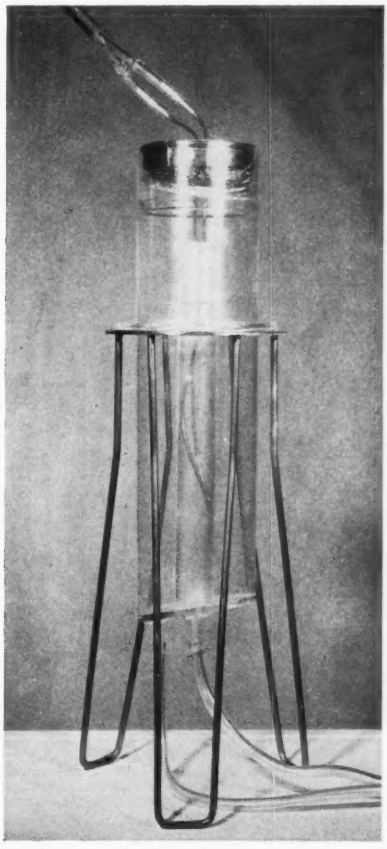


Fig. 1.—This is a photograph of the artificial lung used in these studies. Note the oxygen catheters leading into the inner foaming chamber, the outer receiving chamber, and the metal mesh at the top of the "lung."

serves as a reservoir for the arterialized blood and as a bubble trap. This artificial lung represents a modification of the bubble-type apparatus reported by other investigators.[1, 7, 8, 15, 16]

Venous blood is introduced into the "lung" at the bottom of the inner foaming chamber. Here the blood is exposed to a gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide conveyed from the gas tank via two 14 Fr. oxygen catheters introduced from the top. Bubbles formed as a result

of this interaction rise to the top of the foaming chamber and spill into the outer receiving chamber which has been coated with Antifoam.* A fine mesh stainless steel screen and a metal sponge,† each coated with Antifoam, are placed just above the top of the foaming chamber in the event the column of bubbles should rise to this height. When the bubbles contact the Antifoam, decreased surface tension causes the bubbles to burst. Gas in the center of the bubble which has equilibrated with the excess carbon dioxide in the venous blood then escapes through the top of the "lung." The blood which surrounded the bubble gravitates to the bottom of the reservoir. The bubble-free oxygenated blood is then ready to be pumped back into the arterial tree of the patient. Diagrammatic scheme of the circuit is shown in Fig. 2.

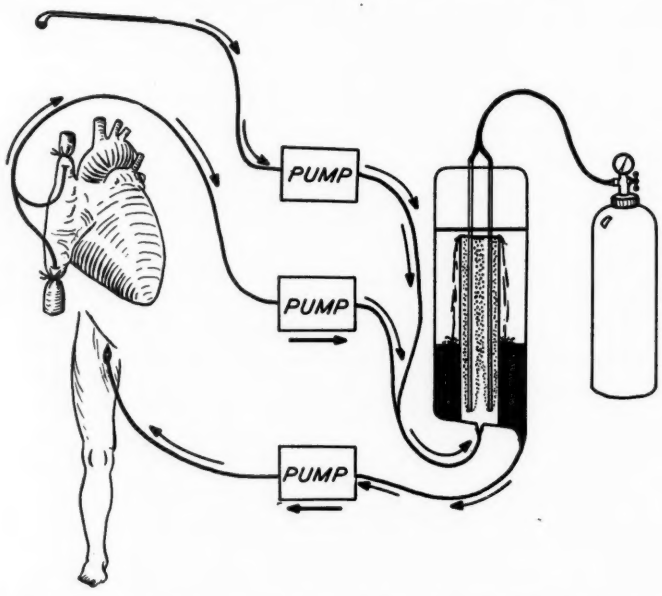


Fig. 2.—This is a schematic representation of the extracorporeal circulation employed. Blood from the vena cava and from the cardiotomy suction is pumped into the foaming chamber where it is mixed with 95 per cent oxygen and 5 per cent carbon dioxide. The reservoir blood is returned to the arterial system.

The flow rate of gas into the artificial lung has been one liter per 100 ml. blood flow per minute. The blood from the first 5 dogs was exposed to 100 per cent oxygen, resulting in excessive removal of carbon dioxide from the blood and respiratory alkalosis. Therefore, subsequent perfusions were carried out with 95 per cent oxygen and 5 per cent carbon dioxide. To prevent the possibility of air embolism, a sizeable volume of blood, at least 1,000 ml., and preferably 1,500 ml., must be maintained in the reservoir at all times.

*Dow-Corning Co., Midland, Michigan.
†Metal Textile Corporation, Roselle, New Jersey.

The artificial oxygenator and the supporting brass ring stand are sterilized by autoclaving. Careful positioning is necessary during autoclaving because of the tendency of the Lucite to melt and become distorted.

3. The tubing used is polyvinyl, a transparent plastic material, which is also sterilized by autoclaving. On the venous side of the circuit, the tubing measures 1/4 inch I.D. and on the arterial side, 3/16 inch I.D. Catheters for withdrawing and returning the blood likewise are of flexible plastic which are autoclaved after being placed in open Pyrex tubing to prevent distortion. Sizes of the catheters range from 10 Fr. to 22 Fr., depending on the diameter of the vessel to be cannulated.

4. Connectors and adaptors are of stainless steel with smooth tapered interior surfaces.

5. An accessory Sigmamotor pump is employed to return the coronary sinus and Thebesian venous blood encountered during the open cardiotomy. This is returned to the venous side of the apparatus, oxygenated, and then recirculated as shown in Fig. 2.

B. *Experimental Procedure.*—

Seventeen dogs ranging in weight from 12 Kg. to 25 Kg. were operated upon with a view toward survival. Perfusion was accomplished by aspirating blood through catheters placed in the superior vena cava via the azygos vein, and the inferior vena cava, reached by way of the right auricular appendage. Blood was returned into the abdominl aorta by introducing a plastic tube into the superficial femoral artery. Perfusion flow rates were between 20 to 35 ml. per Kg. per minute.

Intravenous Nembutal or Pentothal sodium was used for anesthesia. Thoracotomy was performed through the right fifth intercostal space or anterior bilateral intercostal incision transecting the sternum. Positive pressure respiration was used in the open chest surgery.*

After cardiac by-pass was instituted, a long incision was made into the chamber of the right ventricle or the right atrium or both, which incisions were held open up to thirty minutes. The incisions in the heart were then repaired with running 3-0 silk sutures. During the by-pass of the heart and lungs, the positive pressure respirator was disconnected and the lungs allowed to deflate.

The animals were heparinized (1.5 mg. per Kg.). Donor blood sufficient to prime the pump and reservoir was collected, using ether for donor anesthesia and 20 mg. heparin per 500 ml. for anticoagulation. Protamine sulfate was used to counteract the heparin effect at the conclusion of the perfusion. Dosage employed was equivalent to that of the heparin previously administered.

Catheter drainage of the pleural cavity was maintained for two to four hours postoperatively until the dogs had recovered from the anesthesia.

*The authors gratefully acknowledge the help of Dr. Mary Googe as anesthesiologist in the experimental and clinical procedures reported.

RESULTS

A. *Mortality Figures.*—

Fourteen of the dogs thus treated still survive, ranging now from ten to three months following the operation. One dog succumbed on the fifth postoperative day of canine distemper, a condition evident preoperatively and confirmed by microscopic study. One of the initial dogs died of generalized wound oozing.

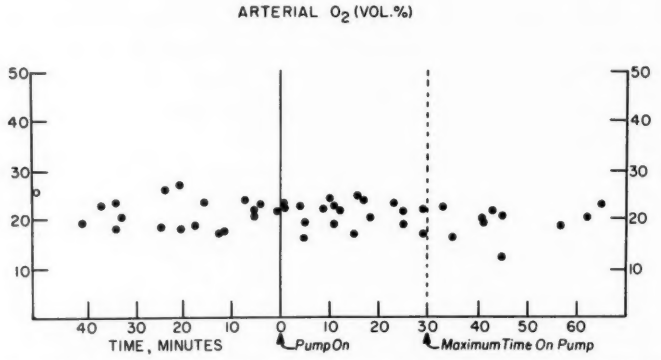


Fig. 3.—This figure plots the values for arterial oxygen saturation, reported as volumes per cent at times indicated in minutes before, during, and after cardiac by-pass. It is evident that adequate oxygen saturation was maintained throughout the experiments.

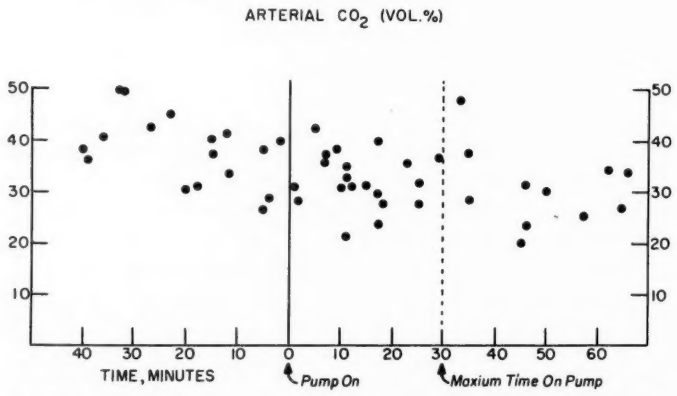


Fig. 4.—The values for carbon dioxide concentrations are recorded as volumes per cent at various times during the experiment. Note that the points for values obtained during the cardiac by-pass fall within the range for values determined before and after the by-pass.

At that time, the artificial lung was made of glass. No similar complication has been observed since changing to Lucite. The third fatality was due to an inadvertent overdose of Nembutal.

B. *Physiologic Data.*—

1. Arterial oxygenation was monitored by a direct recording oximeter with samples obtained from an indwelling catheter in the carotid artery. Frequent

samples were analyzed by the technique of Van Slyke. Values obtained before, during, and after the period of cardiac by-pass are indicated in Fig. 3. This was shown to represent virtually 100 per cent oxygen saturation of all samples.

2. The arterial carbon dioxide concentration, determined by the Van Slyke technique, was measured at intervals throughout the procedure. The data obtained are plotted on Fig. 4.

The mean values for oxygen and carbon dioxide concentrations are shown in Fig. 5, indicating maintenance of physiologic levels of gas concentrations during extracorporeal circulation.

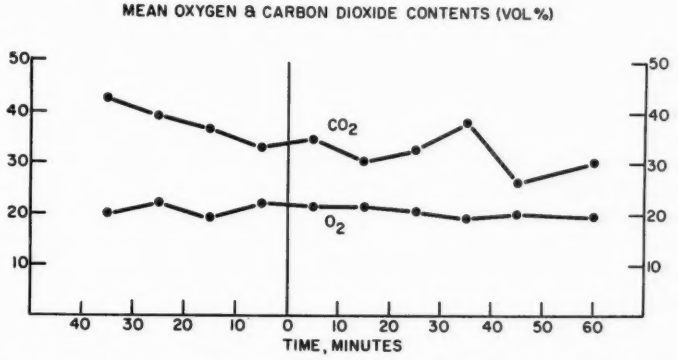


Fig. 5.—Mean values for oxygen and carbon dioxide levels are plotted above.

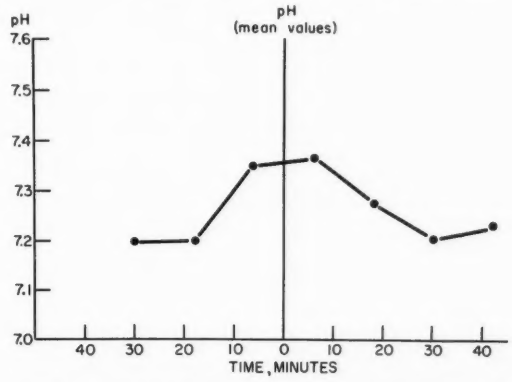


Fig. 6.—The mean values for pH show essentially the same variation during the period of the perfusion as in the pre- and postperfusion intervals of open chest surgery.

3. Arterial pH determinations are depicted in Fig. 6.

4. Plasma hemoglobin values consistently rose to a level of 120 mg. per cent at the conclusion of thirty minutes' perfusion.

5. Electrocardiographic patterns were monitored throughout the experiments and have shown the expected transient injury patterns and firing of ectopic foci associated with the intracardiac manipulations. As long as

manipulation of the interventricular septum was avoided, no serious arrhythmias were encountered. The body temperature was not lowered in the belief that the heart at normal temperatures is less likely to develop dysrhythmias. Pulse pressure contours were recorded using an optimally damped strain gauge galvanometer system. The records indicated that the arterial systolic pressure was maintained in the range of 70 to 90 mm. Hg during the period of perfusion. None of the dogs has exhibited any discernible renal, neurological, or other sequelae. The 14 survivors are evidently normal in every respect.

DISCUSSION

From the foregoing data, it is evident that by the use of this relatively simple oxygenator, flow rates ranging from 280 ml. per minute to 780 ml. per minute can be handled in dogs, maintaining arterial oxygen, carbon dioxide, and pH values within the range of variation observed before and after the perfusion. By this technique, it has been possible to open the right ventricle, right atrium, or both chambers for periods up to thirty minutes, with a regular incidence of permanent survival. The thirty-minute period was chosen for study inasmuch as most intracardiac defects can comfortably be handled in that time.[13]

This method of cardiac by-pass differs essentially from others in the simplicity and effectiveness of the gas exchange chamber. Even larger flow rates (up to 4,500 ml. per min.) are possible by merely modifying the pump and increasing the height of the foaming and receiving chambers of the oxygenator. These revisions are currently being evaluated in this laboratory.

CLINICAL APPLICATIONS

The use of this apparatus for human intracardiac surgery will be reported in detail elsewhere[17] but may briefly be cited here. To date, 5 patients have had direct-vision open heart surgery during perfusion by this means. The results are summarized in Table I.

TABLE I. HUMAN INTRACARDIAC SURGERY WITH BY-PASS TECHNIQUE

AGE	WEIGHT (KG.)	DIAGNOSIS	PROCEDURE	MINUTES ON BY-PASS	OUTCOME
39	57	Atrial septal defects (2)	Direct suture	7	Survived*
8	28	Atrial septal defect with pulmonary hypertension	Direct suture	8	Survived
31	59	Common atrium	Direct suture	20	Survived
4	13	Pulmonic stenosis	Open valvuloplasty	15	Survived
7	16	Tetralogy of Fallot	Open valvuloplasty and suture of vent. septal defect	24	Died†

*Operation performed Nov. 9, 1955.
†Died 2½ days postoperatively—renal failure.

During each of these operations, the oxygen saturation was assessed by means of the ear oximeter, and found to be maintained at normal levels as long

as the flow rate of gas was approximately one liter for each 100 ml. flow of blood per minute. Maximum flow in human perfusions has been 2,100 ml. per minute.

CONCLUSIONS

Extracorporeal circulation for open heart surgery has been accomplished by means of a simplified plastic bubble-type artificial lung in conjunction with the Sigmamotor cross circulation pump. All of the apparatus which comes in contact with blood is autoclaved. Fourteen of 17 dogs subjected to open cardiotomy for periods up to thirty minutes still survive. Analysis of blood oxygen, carbon dioxide, pH, plasma hemoglobin, electrocardiographic and pulse pressure data indicates that physiologic ranges are preserved. Flow rates up to 2,100 ml. per minute have been used. Brief reference has been made to the use of the apparatus in 5 patients for corrective open heart surgery.

ADDENDUM

Since this paper has been presented, the apparatus has been somewhat revised. A new Sigmamotor pump has been employed which uses a ¾ inch I.D. rubber tubing in the pumping chamber, thereby increasing the pumping capacity to 4,800 ml. per minute.

The oxygenating chamber has been enlarged to 34 inches in height and is made of glass. All surfaces are carefully siliconed. No undesirable sequellae have been observed from this change. This eliminates the problem of distortion of the chamber associated with autoclaving.

Hemolysis has been reduced by minimizing the turbulence in the bubbling column. This has been accomplished by introducing the stream of gas into the bottom of the bubbling column through a thin rubber diaphragm perforated with many tiny holes.

REFERENCES

1. Clowes, G. H. A., Neville, W. E., Hopkins, A., Anzola, J., and Simeone, F. A.: Factors Contributing to Success or Failure in the Use of a Pump Oxygenator for Complete By-Pass of the Heart and Lung, Experimental and Clinical, Surgery **36**: 557-579, 1954.
2. Cohen, M., and Lillehei, C. W.: A Quantitative Study on the "Azygos Factor" During Vena Caval Occlusion in the Dog, Surg., Gynec. & Obst. **98**: 225, 1954.
3. Dennis, C., Spreng, D. S., Nelson, G. E., Karlson, K. E., Nelson, R. M., Thomas, J. V., Eder, W. P., and Varco, R. L.: Development of a Pump-Oxygenator to Replace the Heart and Lungs; An Apparatus Applicable to Human Patients, and Application to One Case, Ann. Surg. **134**: 709, 1951.
4. DuShane, J. W., Kirklin, J. W., Patrick, R. T., Donald, D. E., Terry, H. R., Burchell, H. B., and Wood, E. H.: Ventricular Septal Defects With Pulmonary Hypertension, J. A. M. A. **160**: 950, 1956.
5. Gibbon, J. H., Jr.: Discussion of Warden, Cohen, Read, and Lillehei.[19]
6. Gibbon, J. H., Jr.: Application of a Mechanical Heart and Lung Apparatus to Cardiac Surgery, in Recent Advances in Cardiovascular Physiology and Surgery (A Symposium presented by the Minnesota Heart Association and the University of Minnesota, September, 1953), Minneapolis, University of Minnesota, 1954, pp. 107-113.
7. Gollan, F., Grace, J. T., Schell, M. W., Tysinger, D. S., and Feaster, L. B.: Left Heart Surgery in Dogs During Respiratory and Cardiac Arrest at Body Temperatures Below 10° C., Surgery **38**: 363-372, 1956.
8. Helmsworth, J. A., Clark, L. C., Jr., Kaplan, S., Sherman, R. T., and Largen, T.: Artificial Oxygenation and Circulation During Complete By-Pass of the Heart, J. THORACIC SURG. **24**: 117-133, 1952.
9. Jones, R. E., Donald, D. E., Swan, H. J. C., Harshbarger, H. G., Kirklin, J. W., and Wood, E. H.: Apparatus of the Gibbon Type for Mechanical Bypass of the Heart and Lungs, Proc. Staff Meet. Mayo Clin. **30**: 105, 1955.

10. Kirklin, J. W., DuShane, J. W., Patrick, R. T., Donald, D. E., Hetzel, P. S., Harshbarger, H. G., and Wood, E. H.: Intracardiac Surgery With the Aid of a Mechanical Pump-Oxygenator System (Gibbon Type): Report of Eight Cases, Proc. Staff Meet. Mayo Clin. **30**: 201, 1955.
11. Lillehei, C. W., Cohen, M., Warden, H. E., Ziegler, N. R., and Varco, R. L.: The Results of Direct Vision Closure of Ventricular Septal Defects in Eight Patients by Means of Controlled Cross Circulation, Surg., Gynec. & Obst. **101**: 446, 1955.
12. Lillehei, C. W., Cohen, M., Warden, H. E., Read, R. C., Aust, J. B., DeWall, R. A., and Varco, R. L.: Direct Vision Intracardiac Surgical Correction of the Tetralogy of Fallot, Pentalogy of Fallot, and Pulmonary Atresia Defects. Report of First Ten Cases, Ann. Surg. **142**: 418, 1955.
13. Lillehei, C. W., Cohen, M., Warden, H. E., and Varco, R. L.: The Direct Vision Intracardiac Correction of Congenital Anomalies by Controlled Cross Circulation, Surgery **38**: 11, 1955.
14. Lillehei, C. W., DeWall, R. A., Read, R. C., Warden, H. E., and Varco, R. L.: Direct Vision Intracardiac Surgery in Man Using a Simple, Disposable Artificial Oxygenator, Dis. Chest **29**: 1, 1956.
15. Melrose, D. G.: A Mechanical Heart-Lung for Use in Man, Brit. M. J. **II**: 57, 1953.
16. Miller, J.: A Mechanical Heart and Turbulence Oxygenator, Circ. Research **3**: 159-164, 1955.
17. Nelson, R. M., Hecht, H. H., Hardy, R. W., McQuarrie, D. G., and Burge, J.: Intracardiac Direct Vision Surgery Using Extracorporeal Circulation With a Simplified Bubble-Type Oxygenator (in preparation).
18. Warden, H. E., Read, R. C., DeWall, R. C., Aust, J. B., Cohen, M., Ziegler, N. R., Varco, R. L., and Lillehei, C. W.: Direct Vision Intracardiac Surgery by Means of a Reservoir of "Arterialized Venous" Blood, J. THORACIC SURG. **30**: 649, 1955.
19. Warden, H. E., Cohen, M., Read, R. C., and Lillehei, C. W.: Controlled Cross Circulation for Open Intracardiac Surgery, J. THORACIC SURG. **28**: 331, 1954.

A MECHANICAL PUMP-OXYGENATOR FOR DIRECT VISION REPAIR OF ATRIAL SEPTAL DEFECTS

BERNARD S. LEVOWITZ, M.D. (BY INVITATION), MELVIN M. NEWMAN, M.D., JACKSON H. STUCKEY, M.D. (BY INVITATION), MARIE C. KERNAN, M.D. (BY INVITATION), HARRY N. ITICOVICI, M.D. (BY INVITATION), AND CLARENCE DENNIS, M.D., PH.D.
BROOKLYN, N. Y.

THE desire for a direct vision surgical approach to intracardiac defects has stimulated the development of mechanical pump-oxygenators. The various extracorporeal circuits now available have been designed to deliver pulsatile or continuous flows of blood oxygenated by filming,[1, 2] bubbling,[3] dialysis,[4] and passage through the isolated lung.[5] Failure of many of these by-pass systems to gain wider clinical application has been due to the potential hazards associated with the use of them. Air embolism of extra- and intracardiac origin and hemorrhage constitute the principal dangers to the recipient.

The extracorporeal circuit described in this report, a modification of an earlier model,[6] has been used extensively in experimental procedures to investigate these problems.[7, 8] Additional studies were conducted to re-define the acute metabolic changes in animals undergoing total by-pass, since the physiologic alterations suggested by previous results were not in accord with our current concepts. The material in this presentation deals with our experience in the creation and repair of interatrial septal defects in 31 dogs and the successful application of the pump-oxygenator to a clinical case.

METHOD

Mongrel dogs, weighing 8 to 35 Kg., were anesthetized with intravenous pentobarbital sodium, intubated, and placed on a mechanical respirator. Surgery was performed aseptically. The chest was entered through the bed of the right fifth rib (first 12 dogs) or transsternally in the fourth intercostal space (19 dogs). The azygos vein was ligated in continuity. The left subclavian artery was exposed and divided distally. After the pericardium had been widely incised, the inferior and superior venae cavae were isolated extrapericardially and surrounded by sling ligatures. Hemostasis was obtained by the use of electrocautery. Heparin (Connaught Laboratories), 2.5 mg. per kilogram, was administered intravenously at the completion of all dissections.

During this initial preparation, the extracorporeal circuit, which has been reported previously in detail,[7] was assembled (Fig. 1). The flowmeter was

From the Department of Surgery, State University of New York, College of Medicine at New York City, Brooklyn, and the University Division, Kings County Hospital.

Supported by grants from the United States Public Health Service, the Life Insurance Medical Research Fund and the State University of New York.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

an electromagnetically recording rotameter.[10] The rate of venous outflow was recorded on a Sanborn Poly-Viso. The venous blood was delivered to rubber jets placed near the axis of the oxygenator and filmed on four rotating discs. Venous drainage was assisted by a siphon effect equal to the vertical distance between the venae cavae and the openings of the jets (*A* to *B* in Fig. 1); this measured 40 cm. in most animals. The oxygenator tank was continuously flushed by 100 per cent oxygen. The bubble trap contained stainless

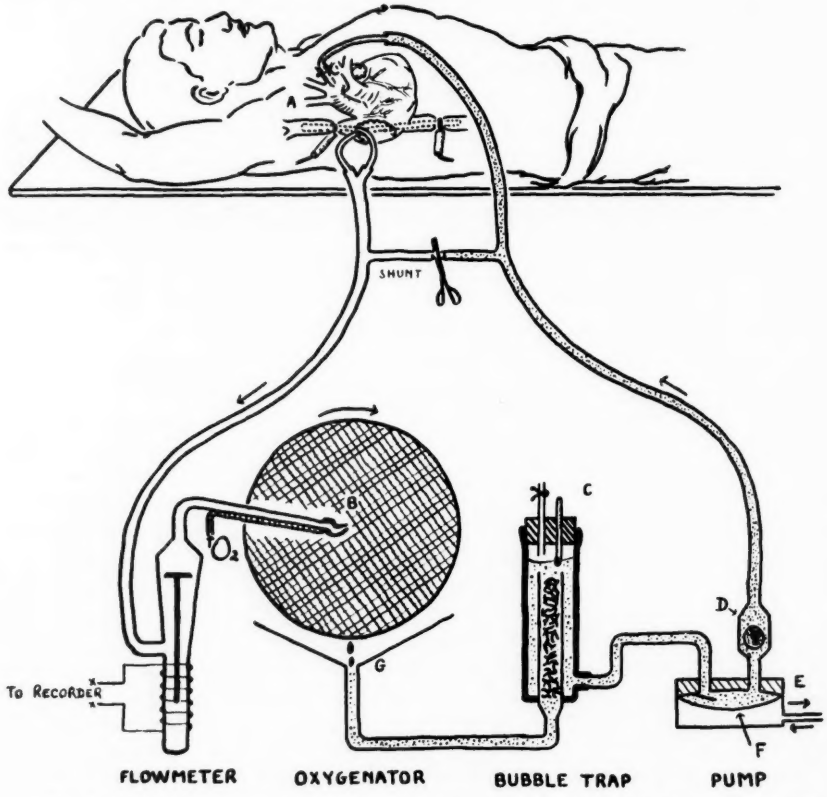


Fig. 1.—Diagram of pump-oxygenator assembly for total body perfusion. *A*, Catheters in place in the left subclavian artery and in the superior and inferior venae cavae. *B*, Rubber jets film the blood on rotating discs above oxygen inlet. C, Outlet for removing air accumulated in bubble trap and thermometer for recording blood temperature. *D*, Nylon shuttle valve prevents regurgitation into pump. *E*, Compressed air from solenoids motivates diaphragm, *F*, of pump which is filled by hydrostatic pressure of blood column, *G*.

steel scouring sponge, coated with Antifoam-A (Dow Corning), within the inner cylinder.[3] It served effectively both as a bubble remover and as a filter for fibrin. In no instance in these experiments was the extracorporeal origin of air embolism implicated. The modified Dale-Schuster pumps[11] were activated by compressed air regulated by solenoid valves. A pulsatile stream, 14 to 17 ml. per stroke, was delivered to the systemic circulation. Filling of

the pumps was dependent upon the displacement of rubber diaphragms by the hydrostatic pressure of the column of blood (*G* in Fig. 1) from the oxygenator. "Gravity filling" eliminated the negative phase in the pumping cycle and prevented air above the blood level in the oxygenator from entering the arterial side of the extracorporeal circuit. The pumps were therefore self-regulatory, accelerating when the influx of blood was increased and slowing as the flow decreased. This minimized gross fluctuations in the holdup volume.[12] For any single perfusion, the stroke output was fixed and the minute volume varied directly as the rate. In anticipation of high flows in large subjects (over 40 Kg.), the capacity of the system was increased by incorporating two bubble traps and using two larger pumps with stroke outputs of 85 ml. The principal limiting factor in achieving these high flows was the caliber of the cannula capable of being threaded into the artery of the recipient.

Freshly drawn, unmatched blood, heparinized with 30 mg. per 1,000 ml., was obtained from donor dogs for priming the extracorporeal circuit (1,100 ml.) and replacement of operative losses. The femoral vein and artery were used for drainage and return of blood in the first 9 animals. In subsequent procedures, the left subclavian artery was cannulated with a plastic catheter (OD ⊣ 14 Fr.).* Similar catheters were placed in the superior and inferior venae cavae through the right auricular appendage with the tips positioned distal to the sling ligatures. A shunt (see Fig. 1) connecting the efferent and afferent limbs of the extracorporeal circuit provided a method for removing residual air bubbles from the system before perfusion.

Blood pressure in the femoral artery and venous pressure in the external jugular vein were monitored by Statham strain gauges recording on a Sanborn Poly-Viso. The electrocardiogram was observed on an oscilloscope throughout the procedure. Prior to and again at the end of the by-pass, blood samples were obtained for determinations of the pH, CO_2, oxygen content of arterial and venous blood, hemoglobin, hematocrit, free plasma hemoglobin,[13] total protein, albumin, fibrinogen, pyruvic acid, plasma chloride, and protamine titre.[14] The analytical methods used for blood chemistry have been recorded elsewhere.[9]

The animal was placed on partial perfusion by occluding the shunt and opening the cannulae (see Fig. 1). Total perfusion was obtained by tightening the sling ligatures about the venae cavae. The heart was allowed to empty for 15 seconds. A 5 centimeter incision was made in the wall of the right atrium from the junction with the inferior vena cava parallel to the atrioventricular groove (Fig. 2). The coronary sinus, tricuspid valve, and crista terminalis were identified. A 2 to 2.5 centimeter incision was made in the interatrial septum. This was confirmed by the appearance of arterialized blood. Rapid suction was used to remove blood draining into the operative site from the left atrium, coronary sinus, and anterior cardiac veins. Frequently, this was returned to the extracorporeal circuit as losses accumulated. The septal incision was closed with interrupted silk sutures and the right atrial wall with a continuous silk suture.

*A beveled curved metal cannula was used for arterial cannulation in the first 17 animals.

Throughout the by-pass, efforts were made to maintain the blood volume at pre-perfusion levels. As they occurred, suction and other operative losses were corrected via the arterial side of the circuit by direct replacement into the oxygenator. In the presence of hypervolemia, a measured quantity of blood was permitted to drain back into the oxygenator. Size of the heart and venous and arterial pressures were guides to the restoration of a normal circulating volume. Protamine (diluted twentyfold with five per cent glucose in distilled water) was administered intravenously over a 15-minute period following decannulation. The dose was dictated by the protamine titer obtained at the end of perfusion. Blood losses incurred subsequent to this stage in the procedure were replaced by direct transfusions of fresh whole blood.

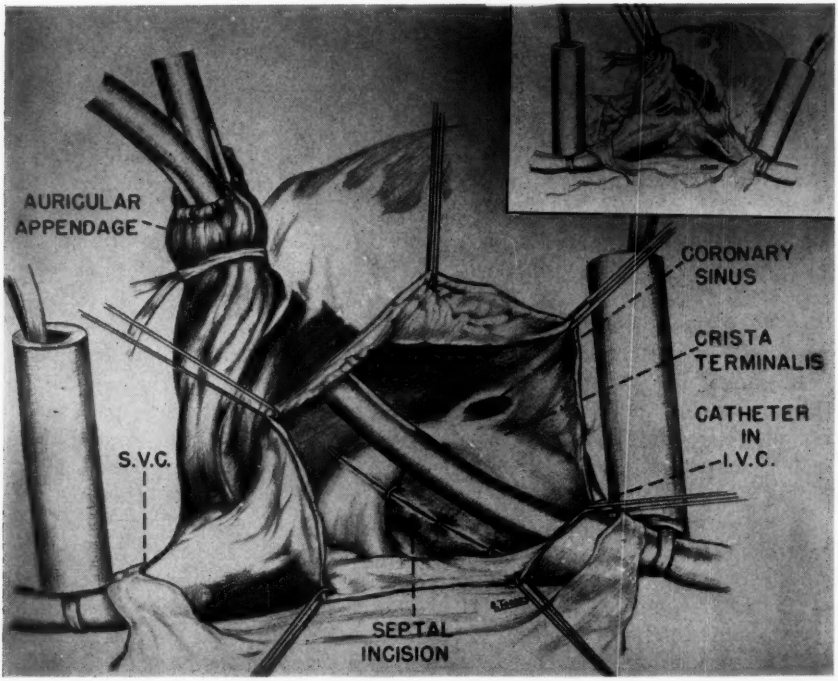


Fig. 2.—Exposure of the interatrial septum through the right atrium. The catheter can be displaced to facilitate the approach to the septum. *Inset;* Type of incision employed in atriotomy.

Large-bore thoracostomy tubes were placed in both pleural cavities and connected to waterseals. The pericardium was loosely approximated and the chest wound closed in layers. Postoperatively, the animals were observed with regard to adequacy of ventilation, chest drainage, body weight, blood pressure, rectal temperature, and reaction from anesthesia. To correct the mild hypothermia produced during the by-pass, the animals were rewarmed on blankets.* Vigorous efforts were made to evacuate blood and air from the pleural

*Therm-O-Rite Products Corp., Buffalo, N. Y.

cavity and encourage lung expansion. Bleeding from the chest was promptly corrected with whole blood transfusions. At regular intervals, fractional protamine titrations were obtained and appropriate doses of protamine administered until the clotting time returned to normal. Persistent chest drainage in the presence of a normal clotting time and absence of circulating heparin was an indication for re-exploration in one animal in which bleeding from the right atrial appendage was corrected. A normal circulating volume at the end of a procedure was reflected in a favorable comparison of pre- and postoperative body weights.

Three techniques were employed to prevent embolization of air through the incised interatrial septum. In 13 dogs a multiperforated vent was placed into the left ventricle through a stab wound in the avascular portion of the apex as recommended by Miller and his co-workers.[15] Aspirated blood and air under a negative pressure of –10 to –20 cm. of water, were returned directly to the oxygenator. In 12 dogs, an attempt was made by positioning the animals to preserve a continuous "lake" of blood or saline solution over the incised septum. Five degrees of Trendelenburg position were used to prevent air emboli from reaching the brain.[16] In 6 animals, ventricular fibrillation was induced with a shock of a 6-volt 60-cycle alternating current through two closely spaced electrodes applied to the ventricular epicardium.[17] Defibrillation was accomplished while the animal was on total perfusion with a countershock of 125 volts for about 0.1 second.

RESULTS

Thirty-one dogs were perfused for periods of 17 to 63 minutes in which time an interatrial septal defect was created and repaired. Rectal temperatures fell progressively during the by-pass. The average decrease was 5.5° C. and varied inversely with the size of the animal and directly with the length of perfusion. In experimental procedures no attempt was made to prevent this decline.

Perfusion pressures (femoral artery pressure) varied between 80 and 100 mm. Hg systolic and 30 and 50 mm. Hg diastolic. Insufficiencies in the circulating volume resulted in a fall in perfusion pressure. Pressure tracings during the perfusion showed secondary waves following ventricular systole. They were most marked in the diastolic phase of the pumping cycle and were abolished by ventricular fibrillation.

The results of analysis of blood oxygen and flows are summarized in Table I. Flows were measured by two methods. The pump rate multiplied by the

TABLE I. OXYGENATION OF BLOOD AND FLOWS AT END OF PERFUSION

	ARTERIAL		VENOUS				
	O_2 CONTENT (C.C./100 ML.)	O_2 SATURATION (PER CENT)	O_2 CONTENT (C.C./100 ML.)	O_2 SATURATION (PER CENT)	A-V DIFF. (C.C./100 ML.)	FLOW (ML./KG./MIN.)	O_2 CONSUMED (C.C./KG./MIN.)
Average	19.63	100.41	8.26	41.95	11.38	33	3.4
S.D.	±2.76	±4.75	±4.02	±14.35	±3.33		
Range							
minimum	12.52	93.05	2.65	17.34	4.23	15	1.2
maximum	23.83	108.74	15.34	62.90	16.71	55	6.2

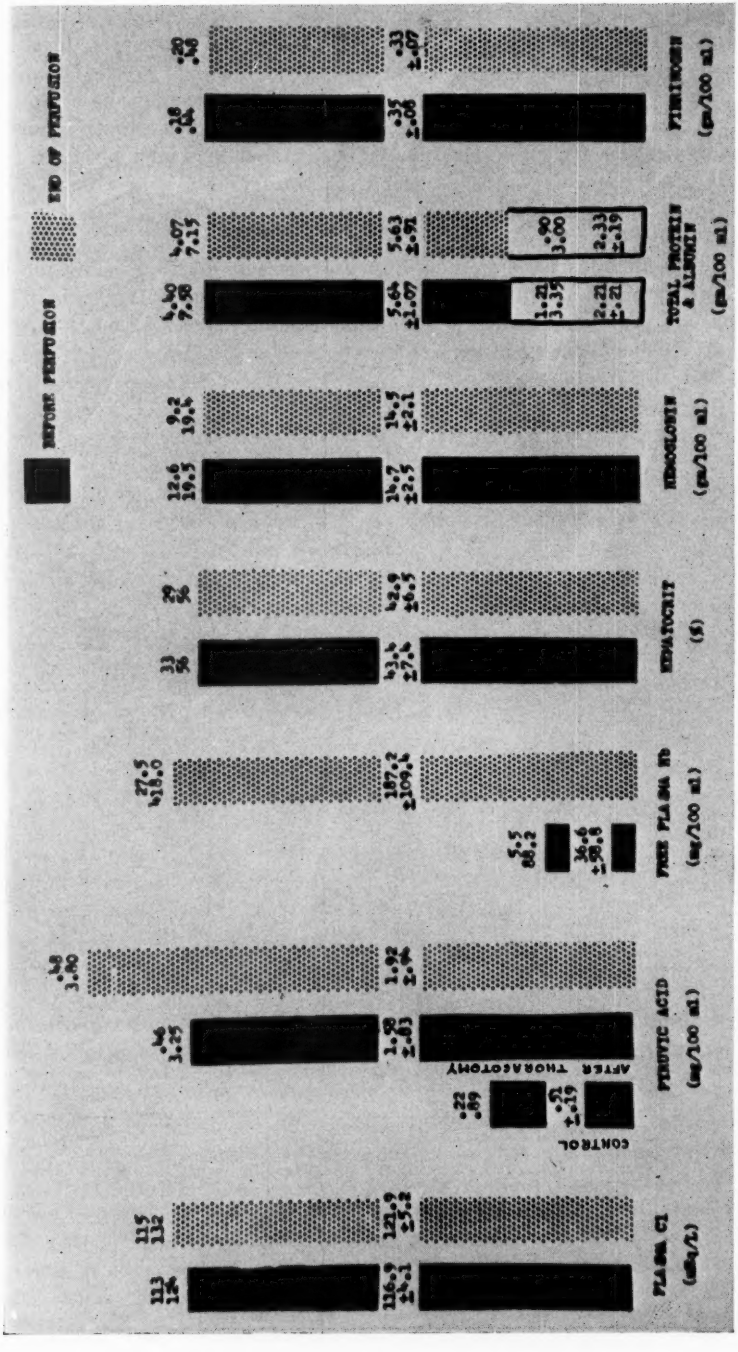


Fig. 3.—Results of blood determinations. (Figures at top of column represent the range of the average value which appears in the middle of the column with the standard deviation.)

stroke output corresponded with the flows recorded by the flowmeter. For 31 dogs this averaged 33 ml. per kilogram per minute (20 per cent of basal cardiac output[18]) and would place this pump-oxygenator in the low flow category. With this reduced turnover of blood, an average of 3.4 c.c. of oxygen per kilogram per minute was delivered to the tissues. This was 40 per cent of the assumed basal oxygen consumption and was attributed to the increase in arteriovenous difference (coefficient of oxygen utilization[19]). The highest oxygen uptake in this series was 102 c.c. per minute in a 34-kilogram animal with a flow of 940 c.c. per minute. This was well within the maximum oxygenating capacity of 130 c.c. per minute established for the rotating disc (four screens) oxygenator at a flow of 2 L. under the standard conditions set forth by Gimbel and Engelburg[12]; raising the oxygen saturation of hemoglobin from 60 per cent to 90 per cent.

In the first ten perfusions, a single phase, positive pressure, mechanical respirator[20] was used. The remaining experiments were conducted with an intermittent positive-negative pressure respirator,* ventilating with 100 per cent oxygen and with a CO_2 absorption cannister in the circuit. The efficiency of dual phase ventilation was displayed in the low pCO_2 and elevated pH in many of the blood samples obtained prior to perfusion.[21] The resulting respiratory alkalosis appeared to have no adverse effects. During perfusion there was a fall in the buffer bicarbonate and a further drop in the pCO_2 (Table II). The effectiveness of CO_2 exchange by the oxygenator is indicated by the arteriovenous CO_2 difference.

TABLE II. CHANGES OF CO_2 AND pH BEFORE AND AT END OF PERFUSION

	BEFORE PERFUSION				END OF PERFUSION					
	ARTERIAL				ARTERIAL				VENOUS	
	CO_2 CONTENT (mM/L.)	pCO_2* (MM. HG)	HCO_3* (MEQ./L.)	pH	CO_2 CONTENT (mM/L.)	pCO_2* (MM. HG)	HCO_3* (MEQ./L.)	pH	CO_2 CONTENT (mM/L.)	A-V CO_2 DIFF. (mM/L.)
Average	13.74	32	15.1	7.32	8.52	18	9.5	7.36	14.50	5.98
S.D.	±5.86			±.65	±2.87			±.69	±3.58	±2.24
Range										
minimum	5.41	13	5.6	7.00	2.77	<10	6.2	7.00	8.15	3.06
maximum	25.41	86	26.1	7.73	18.77	35	13.9	7.73	25.62	14.44

*Determined from nomogram of Singer and Hastings.[34]

Comparison of the pyruvate levels in the donor reservoir and in the recipient animals prior to perfusion demonstrated an average increase of 209 per cent; the average rise during the by-pass was 21 per cent. This is shown graphically in Fig. 3. Blood chloride appeared to rise slightly† and was due, in part, to the incomplete removal of isotonic sodium chloride used for flushing the by-pass circuit free of formaldehyde. The values for free plasma hemoglobin exceeded the levels mentioned in previous reports from this laboratory.[7] The practice of replacing excessive operative losses with blood retrieved by suction (average free plasma hemoglobin—222 mg. per 100 ml.) was implicated. Total

*Air-Shields, Inc., Hatboro, Pa.

†P value for difference between control and perfusion samples was .06.

protein and fractions were not altered significantly by perfusion. This has been confirmed by plasmaphoretic studies.[22] Hematocrit and hemoglobin were unchanged (see Fig. 3).

In the presence of a normal, reduced, or augmented circulating volume in the recipient, the venous pressure was positive when the drainage capacity of the caval catheters was less than the return to the heart and was negative if the capacity of the catheters exceeded the return. Successful perfusions were conducted under both conditions. As the most sensitive indicator of variations in the circulating volume, the venous pressure responded to changes of less than 50 ml. Fluctuations in the flowmeter curve, level of blood in the oxygenator, blood pressure and stroke rate of the pumps corresponded, to a lesser degree, with those in the venous pressure. These indices were used to maintain the circulatory volume during perfusion.

The average blood loss was 1,050 ml. (range, 125 ml. to 2,300 ml.). The average replacement was 1,300 ml. Perfusion and postoperative chest losses averaged 630 and 370 ml., respectively. A comparison of pre- and postoperative weights revealed a positive blood balance in the majority of perfusions.

The clotting time in 22 animals was restored to normal in an average period of two hours by a single dose of protamine. Additional increments were required in 9 animals. Thirty of the 31 dogs had normal clotting times by the fifth postperfusion hour. The average initial dose of protamine required for neutralization of circulating heparin was 4.6 mg. per kilogram. The absence of stoichiometric neutralization of the original heparinizing dose was attributed to the variation in potency of protamine lots and emphasized the need for titrations to arrive at the correct dosage.

Table III summarizes the data on fibrillation. The reversibility of coronary air embolism is shown in Table IV and was in accord with the work of Geoghegan and Lam.[23] The results indicated that neither body positioning nor the introduction of a ventricular vent provided complete protection from this hazard. Coronary air embolism was not observed in any of the 6 dogs in which fibrillation was deliberately induced. Incision through the septum into the left atrium in this group was accompanied by a continuous, occasionally vigorous,

TABLE III. VENTRICULAR FIBRILLATION

CAUSE		PERIOD OF FIBRILLATION (MIN.)	DEFIBRILLATION	SURVIVOR	CAUSE OF DEATH
Placement of vent	1	28	1	1	
Coronary air embolism	4	14-41	3	2	Cerebral air embolism, cardiac standstill
Induced	6	14-34	6	6	

flow of arterialized blood from the left side. This was not observed in those hearts contracting regularly. Frequently, the blood level in the left atrium was displaced by air and remained below the incised septum. The diagnosis of coronary air embolism was established by direct inspection of coronary arteries and was confirmed by disturbances in rhythm, mottling and cyanosis

TABLE IV. AIR EMBOLISM

DOG NUMBER	SOURCE OF AIR	PROPHYLAXIS	ECG	RESULTS	SURVIVAL
83	Septal defect	Vent	Ventricular fibrillation	Coronaries cleared of air, defibrillated	Survivor
100	Septal defect	Vent	No change	Coronaries cleared of air	Died 12 hours postperfusion of hemorrhage
300*	Septal defect	Vent	Current of injury	Reverted to normal ECG	Died at operation of cerebral air embolism
201	Septal defect	Vent	No change	Coronaries cleared of air	Died 18 hours postperfusion of cerebral air embolism
433	Septal defect	Position	Ventricular fibrillation	Coronaries cleared of air, defibrillated	Died 48 hours postperfusion of cerebral air embolism
475	Septal defect	Position	Ventricular fibrillation	Coronaries cleared of air, defibrillated	Survivor
469	Catheter in left ventricle	Position	Ventricular fibrillation	Coronaries cleared of air, heart into standstill	Died at end of perfusion

*No air noted in coronary vessels.

of the myocardium. Clearance of air from the coronary vessels was accelerated by raising the perfusion pressure (increasing the air pressure activating the pumps), augmenting the circulating volume, cardiac massage, and compression of the aorta distal to the subclavian cannula. Three of the 6 animals whose hearts were returned to normal sinus rhythm succumbed to cerebral air embolism (see Table IV).

There were 22 survivors in thirty-one perfusions. Four of nine deaths were attributed to air embolism. One of the animals (433) survived for 48 hours and demonstrated opisthotonos, extensor rigidity, hyperreflexia, and hyperirritability. Vascular changes associated with cerebral air embolism were observed at autopsy.[24, 25] A dissecting aneurysm in one animal was ascribed to a tear in the intima of the left subclavian artery at the aortic junction, caused by a metal cannula. Two dogs died of intrapleural hemorrhage 12 hours postoperatively. Extensive damage to the interatrial septum and loss of an airway were responsible for two deaths.

There was a late mortality (more than 5 days postoperative) consisting of 10 dogs. These deaths, for the most part, were caused by wound infection with empyema. Two of these were secondary to sternal separations of transsternal incisions. One animal which was perfused through the femoral artery and vein developed congestive heart failure and pulmonary edema. Autopsy disclosed that a margin of the septal incision had been sutured to the "valve" of the inferior vena cava, shunting the blood from it into the left atrium. Severe stenosis of the inferior vena cava due to the atrial wall suture was the cause of death in another animal. The use of the right atrium for placement of caval catheters which serve as guides during suture, has prevented repetition of these errors. An infected thrombus adherent to the septal suture line was found in another animal with empyema.

Gross examination of the hearts of all but 2 of the 12 animals sacrificed at intervals up to eight months disclosed healed, smoothly endothelized intra-

cardiac incisions. A thickened mural plaque and a calcified pedunculated thrombus, both overlying the septal suture line, were seen in 2 animals. Inspection of the abdominal viscera revealed no evidence of recent or healed infarcts.

On the basis of these experimental investigations, the apparatus was employed in a clinical case.

CASE REPORT

J. B., an 18-year-old girl, a known "cardiac" since the age of one year, complained of limited exercise tolerance, exertional dyspnea, and precordial pain. On admission to the hospital, physical examination revealed a well-developed white female (53 Kg.) who presented a left precordial bulge. There was a harsh systolic murmur (Grade 3) heard loudest over the pulmonic area; the second pulmonic sound was diminished. No cyanosis or clubbing was noted. Chest x-ray showed enlargement of the right ventricle with a prominent left heart border. The electrocardiogram revealed a right ventricular strain pattern. Angiography demonstrated simultaneous opacification of the pulmonary artery and aorta. Catheterization data* are summarized in Table V. They were interpreted as

TABLE V. CATHETERIZATION DATA—PATIENT J. B.

	PREOPERATIVE		POSTOPERATIVE	
LOCATION OF SAMPLE	PRESSURE (MM. HG)	O_2 CONTENT (C.C./100 ML.)	PRESSURE (MM. HG)	O_2 CONTENT (C.C./100 ML.)
Pulmonary capillary	11	16.0	10	15.7
Pulmonary artery	20/12	15.4	23/13	11.9
Right ventricle (infundib.)	27/10	15.8	-	-
Right ventricle (sinus)	60/0	-	37/0	11.5
Right atrium	10	14.7	10	11.6
Superior cava	-	11.9	-	9.5
Brachial artery	-	16.0*	-	15.9†
Brachial artery (after exercise)	-	15.6‡		
Pulmonary blood flow	7.5 L./min.		5.8 L./min.	
Systemic blood flow	1.1 L./min.		5.1 L./min.	
Shunt, left-to-right	6.4 L./min.		0.7 L./min.	

*94.3 per cent saturated.
†94.5 per cent saturated.
‡92.0 per cent saturated.

indicating the presence of an interatrial septal defect with pulmonic stenosis of the infundibular type. The predominant shunt was left to right. On exercise, a slight right-to-left shunt was noted. On June 30, 1955, open heart surgery was performed through a transsternal incision. The patient underwent total body perfusion and an atrial cardiotomy was made in the excluded heart. A large foramen ovale type defect, 3 cm. by 5 cm., was obliterated with interrupted sutures. During the repair, a pool of blood was maintained over the defect to prevent air from entering the left side of the heart. Following closure of the right atrium, a 2 cm. incision was made in the right ventricular outflow tract and the right ventricle digitally explored. No infundibular stenosis was detected and the cardiotomy was closed. The patient's heart was excluded for 23 minutes during which time the extracorporeal flow rate averaged 36 ml. per kilogram per minute. The patient was awake at the conclusion of the procedure. Her postoperative course was uneventful and she was discharged on the thirtieth hospital day.

Six months later she was recatheterized. The data (see Table V) indicated a small left-to-right shunt (0.7 L. per minute) which was considered to be of no clinical significance. At this time she was free of exertional dyspnea and was engaging in unrestricted activity.

*Courtesy of Drs. Harold A. Lyons and John J. Kelly.

DISCUSSION

The results of these experiments show that the important metabolic changes occurring in a total by-pass are confined to the factors regulating acid-base balance. The appearance of a metabolic acidosis in perfused dogs has been attributed to a rise in fixed acid.[6, 26, 27] Pyruvic acid levels above 4 mg. per 100 ml. have been associated with a poor prognosis.[9] In this series, the increase in pyruvate was of minimal significance. The fall in bicarbonate buffer (see Table III) indicated that other acid metabolites were accumulating during perfusion. An appreciable increase in lactic acid has been reported.[26] Hyperventilation with a dual phase respirator in the preperfusion period and excessive elimination of CO_2 by the screen oxygenator during the by-pass produced a marked depression of the arterial pCO_2. This served to compensate for the metabolic acidosis, maintain the pH within normal limits and improve the oxygen uptake of hemoglobin (Bohr effect). Similar observations have been made with cross circulation techniques where an increase in the donor respiratory minute volume was used to control the fall in recipient pH.[27] Measures to regulate the pH by the addition of Na HCO_3 or flushing the oxygenator with 5 per cent CO_2 and 95 per cent oxygen were not employed.

Hemoglobinemia in hypotensive states has been recognized as a cause of renal damage in man.[28] However, under low perfusion pressures such as obtained in these experiments, no ill effects were noted even when the free plasma hemoglobin levels were in excess of 400 mg. per 100 ml. The recent adoption of a low-vacuum, variable suction pump has avoided foam formation and reduced the red cell destruction in the aspirated blood returned to the circuit.

In our experience the prime requisite for control of postperfusion hemorrhage and the restoration of normal clotting was complete reversal of heparinemia with protamine. Fractional protamine titrations obtained at regular intervals in the recovery period indicated reduced but significant concentrations of circulating heparin (5 to 10 mcg. per milliliter) which prevented normal clotting.[14] The existence of a heparin rebound phenomenon has been postulated to explain the persistence of circulating heparin despite adequate neutralizing doses of protamine.[4] The role of the fresh whole blood transfusion requires further evaluation. In early experiments it was given routinely at the completion of the by-pass to replace destroyed clotting factors, equalize postoperative losses and avoid the introduction of other anticoagulants. More recent evidence indicates that with a normal or slightly positive blood balance at the end of perfusion, adequate protamine dosage alone will restore the clotting time. Protracted perfusions (over one hour) appear to enhance postoperative bleeding. The hemorrhagic deaths in 2 dogs early in this series were ascribed to abnormal hemolytic and proteolytic activity due to plasma fibrinolysin[29] or bacterial contamination.[30] The impression has since been gained that these deaths can be averted by stricter attention to the details of postoperative care.

Exposure of the left side of the isolated contracting heart to the atmosphere directly or through septal defects predisposes to systemic air embolism. In 6 animals, incisions into the interatrial septum were accompanied by the entry of air into the left atrium and left ventricle in diastole. In the presence of a

competent mitral valve, bronchial artery return admixed with air was ejected into the systemic circulation in systole. Continued circulation through the left side of the heart made it difficult to preserve a level of blood or saline solution in the right atrium over the incised septum. Extracorporeal circuits which employ low perfusion pressures and deliver pulsatile flows are unable to maintain continuous closure of the aortic valves. Ventricular systolic pressure exceeds the perfusion pressure, especially in the diastolic phase of the mechanical pump, and ejection of air and blood into the aorta follows. Cookson and Costas-Durieux,[31] using hypothermia supplemented by arterial transfusions in open cardiotomies, stated that a nonpulsatile flow at a pressure of 70 mm. of Hg prevented opening of the aortic valves in ventricular systole; the technique was not uniformly effective in avoiding air embolism in their animals. Potassium-induced cardiac arrest has been advocated by Melrose and his group.[32] This method requires occlusion of the aorta above the coronary ostia, thereby limiting the period of by-pass and depriving the myocardium of the benefits of continuous perfusion. Miller and associates[15] have employed a left ventricular vent in experimental procedures and in a successful clinical case with an interatrial septal defect. In our hands, this method failed to eliminate coronary and/or cerebral air embolism in 4 of the 13 dogs in which it was used. Previous experience with 5 cases of ventricular fibrillation (4 due to coronary air embolism and one due to placement of a ventricular vent) had demonstrated the excellent protection afforded the heart by uninterrupted perfusion of the coronaries with oxygenated blood (see Table III). Accordingly, fibrillation to abolish ventricular ejection, as first proposed by Glenn and Sewell[33] and Senning,[10] was deliberately induced in 6 dogs with gratifying results. The "sucking action"[33] of the ventricle in diastole was replaced by a persistent flow of blood from the left atrium through the septal defect. Air embolism was not observed. Operative techniques were expedited by the quiet field. Myocardial tone and color remained satisfactory throughout the by-pass. There was a coarse fibrillatory pattern on the electrocardiogram. The hearts were defibrillated with ease soon after closure of the cardiac incisions. Promptness in restoring regular contractions reduced the tendency of the chambers to dilate because of the accumulation of coronary venous and bronchial artery blood. All 6 animals survived and at autopsy showed no myocardial damage attributable to fibrillation. The use of ventricular fibrillation as an adjunct to perfusion in the direct approach to lesions of the left side of the heart is currently being explored.

The available evidence indicates that the venous pressure is a valuable guide to the progress of a perfusion. This study will be presented in a separate paper.

SUMMARY

1. A simplified pump-oxygenator with safeguards against the introduction of air is described.

2. Interatrial septal defects were created and repaired under direct vision in 31 dogs with 22 survivors. During this study, techniques have been developed which appear to have reduced the hazards of total body perfusion.

3. Protamine titrations are an important factor in the control of post-perfusion bleeding.

4. The principal metabolic change during perfusion is the development of a metabolic acidosis. The desirability of a low arterial pCO_2 to counteract this is discussed.

5. The case report of a successful closure under direct vision of an interatrial septal defect in an 18-year-old girl is presented.

6. Deliberately induced ventricular fibrillation can eliminate air embolism during open cardiac surgery.*

The authors wish to acknowledge the catheterization studies performed by Dr. Harold A. Lyons and Dr. John J. Kelly of the Department of Medicine, and the technical assistance of Miss LaVonne A. Young, Mrs. Alva C. Riddick, Mr. Herbert Lauritzen, and Mr. Ludwig Quabeck.

REFERENCES

1. Karlson, K. E., Dennis, C., Westover, D., and Sanderson, D.: Pump-Oxygenator to Supplant the Heart and Lungs for Brief Periods, Surgery **29**: 678, 1951.
2. Miller, B. J., Gibbon, J. H., Jr., and Gibbon, M. H.: Recent Advances in the Development of a Mechanical Heart and Lung Apparatus, Ann. Surg. **134**: 694, 1951.
3. Clark, L. C., Jr., Gollan, F., and Gupta, V. B.: The Oxygenation of Blood by Gas Dispersion, Science **111**: 85, 1950.
4. Kolff, W. J., Effler, D. B., Groves, L. K., Peerboom, G., and Moraca, D. P.: Disposable Membrane Oxygenator (Heart-Lung Machine) and Its Use in Experimental Surgery, Cleveland Clin. Quart. **23**: 69, 1956.
5. Mustard, W. T., and Chute, W. T.: Experimental Intracardiac Surgery With Extracorporeal Circulation, Surgery **30**: 684, 1951.
6. Dennis, C., Spreng, D. S., Jr., Nelson, G. E., Karlson, K. E., Nelson, R. M., Thomas, J. V., Eder, W. P., and Varco, R. L.: Development of a Pump-Oxygenator to Replace the Heart and Lungs; An Apparatus Applicable to Human Patients, and Application to One Case, Ann. Surg. **134**: 709, 1951.
7. Newman, M. M., Stuckey, J. H., Levowitz, B. S., Young, L. A., Dennis, C., Fries, C. C., Gorayeb, E. J., Zuhdi, M., Karlson, K. E., Adler, S., and Gliedman, M.: Complete and Partial Perfusion of Animal and Human Subjects With the Pump-Oxygenator, Surgery **38**: 30, 1955.
8. Stuckey, J. H., Newman, M. M., Dennis, C., Levowitz, B. S., Iticovici, H. N., Gorayeb, E. J., Kernan, M., and Young, L. A.: The Creation and Repair of Interventricular Septal Defects in Dogs Utilizing the Heart-Lung Machine, Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1955.
9. Spreng, D. S., Jr., Dennis, C., Young, L. A., Nelson, G. E., Karlson, K. E., and Pereyma, C.: Acute Metabolic Changes Associated With Employment of a Pump-Oxygenator to Supplant the Heart and Lungs, Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1952, Philadelphia, 1953, W. B. Saunders Co., pp. 165-171.
10. Senning, A.: Ventricular Fibrillation During Extracorporeal Circulation, Acta chir. scandinav. Suppl. 171, 1952.
11. Dale, H. A., and Schuster, E. H.: A Double Perfusion Pump, J. Physiol. **64**: 256, 1928.
12. Gimbel, N. S., and Engelberg, J.: Blood Oxygenators: Theory and Studies in Design, Surgery **35**: 645, 1954.
13. Hunter, F. T., Grove-Rasmussen, M., and Soutter, L.: A Spectrophotometric Method for Quantitating Hemoglobin in Plasma or Serum, Am. J. Clin. Path. **20**: 429, 1950.
14. Allen, J. G., Moulder, P. V., Elghammer, R. M., Grossman, B. J., McKeen, C. L., Sanderson, M., Egner, W., and Crosbie, J. M.: A Protamine Titration As An Indication of a Clotting Defect in Certain Hemorrhagic States, J. Lab. & Clin. Med. **34**: 473, 1949.
15. Miller, B. J., Gibbon, J. H., Jr., Greco, V. G., Cohen, C. H., and Allbritten, F. F., Jr.: The Use of a Vent for the Left Ventricle as a Means of Avoiding Air Embolism to the Systemic Circulation During Open Cardiotomy With the Maintenance of the Cardiorespiratory Functions of Animals by a Pump-Oxygenator, Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1953, Philadelphia, 1954, W. B. Saunders Co., pp. 29-33.

*Since the preparation of this report, induced fibrillation has been employed effectively in the direct vision repair of 2 clinical cases of interventricular septal defect.

16. Van Allen, C. M., Hrdina, L. S., and Clark, J.: Air Embolism From the Pulmonary Vein, Arch. Surg. **19**: 567, 1929.
17. Wiggers, C. J., and Wegria, R.: Ventricular Fibrillation Due to Single Localized Systole, Am. J. Physiol. **128**: 500, 1940.
18. Stewart, G. N.: Output of the Heart in Dogs, Am. J. Physiol. **57**: 27, 1921.
19. Cohen, M., and Lillehei, C. W.: A Quantitative Study of the "Azygos Factor" During Vena Caval Occlusion in the Dog, Surg., Gynec. & Obst. **98**: 225, 1954.
20. Dennis, C., Karlson, K. E., Eder, W. P., Nelson, R. M., Spreng, D. S., Jr., Thomas, J. V., and Nelson, G. E.: A Simple Efficient Respirator and Anesthesia Bag for Open Chest Surgery, Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1950, Philadelphia, 1951, W. B. Saunders Co., pp. 583-588.
21. Gibbon, J. H., Jr., and Haupt, G. J.: The Need for Adequate Pulmonary Ventilation During Surgical Operations, S. Clin. North America **35**: 1553, 1955.
22. Stern, K.: Personal communication.
23. Geoghegan, T., and Lam, C. R.: The Mechanism of Death From Intracardiac Air and Its Reversibility, Ann. Surg. **138**: 351, 1953.
24. Fries, C. C., Karlson, K. E., Adler, S., Levowitz, B. S., Cook, A. W., and Dennis, C.: Brain Changes Associated with Air Embolism, Presented before the Neurosurgical Section at Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1954.
25. Fazio, C., and Sacchi, U.: Experimentally Produced Red Softening of the Brain, J. Neuropath. & Exper. Neurol. **13**: 476, 1954.
26. Cohen, M., Warden, H. E., and Lillehei, C. W.: Physiologic and Metabolic Changes During Autogenous Lobe Oxygenation With Total Cardiac Bypass Employing the Azygos Flow Principle, Surg., Gynec. & Obst. **98**: 523, 1954.
27. Warden, H. E., Cohen, M., DeWall, R. A., Schultz, E. A., Buckley, J. J., Read, R. C., and Lillehei, C. W.: Experimental Closure of Interventricular Septal Defects and Further Physiologic Studies on Controlled Cross Circulation, Proc. Surg. Forum, Clin. Congress Am. Coll. Surgeons, 1954, Philadelphia, 1955, W. B. Saunders Co., pp. 22-28.
28. Maluf, N. S. R.: Factors Inducing Renal Shutdown from Lysed Erythrocytes, Ann. Surg. **130**: 49, 1949.
29. Scott, E. V. Z., Matthews, W. F., Butterworth, C. E., Jr., and Frommeyer, W. B., Jr.: Abnormal Plasma Proteolytic Activity, Surg., Gynec. & Obst. **99**: 679, 1954.
30. Nelson, R. M.: Metabolic Effects of Paracolon Bacteremia, Ann. Surg. **134**: 885, 1951.
31. Cookson, B. A., and Costas-Durieux, J.: The Use of Arterial Transfusions as an Adjunct to Hypothermia in the Repair of Septal Defects, Ann. Surg. **140**: 100, 1954.
32. Melrose, D. B., Dreyer, B., Bentall, H. H., and Baker, J. B. E.: Elective Cardiac Arrest, Lancet **2**: 21, 1955.
33. Glenn, W. W. L., and Sewell, W. H., Jr.: Experimental Cardiac Surgery; IV. The Prevention of Air Embolism in Open Heart Surgery; Repair of Interauricular Septal Defects, Surgery **34**: 195, 1953.
34. Singer, R. B., and Hastings, A. B.: An Improved Method for Estimation of Disturbances of Acid-Base Balance of Human Blood, Medicine **27**: 223, 1948.

ELIMINATION AND TRANSPORT OF MUCUS IN THE LUNG

An Experimental Study

Edward G. Huppler, M.D.* (by invitation), O. Theron Clagett, M.D.,** and John H. Grindlay, M.D.*** (by invitation)
Rochester, Minn.

WHEN a lobar bronchus is completely obstructed or transected in the absence of infection, the lung becomes atelectatic and the major bronchi become filled with mucus. However, the lung does not become a mucocele nor do the bronchi become cystic because of accumulated secretions of the respiratory tract. This is illustrated clinically by cases of traumatic rupture of the bronchus. If the patient survives the early posttraumatic period, the unrepaired ruptured bronchus closes completely and the major bronchi contain viscid, noninfected mucus. Many authors[1-5] have reported cases in which plastic repair of bronchi following traumatic rupture has resulted in ultimate physiologic recovery of the involved lung. This has been confirmed experimentally by Webb and Burford.[6] If infection is superimposed upon obstruction, a cystic form of bronchiectasis results.[7-10]

What happens to mucus and secretions in a lung that has the bronchus transected? It seems that there are two possibilities. If the secretions cannot be removed through the tracheobronchial tree, either they must be eliminated in the lung or the production of secretions must cease.

Some authors[11-19] believe that retained secretions are important in the pathogenesis of pulmonary cysts of the bronchogenic type. Alveolar agenesis has been observed in the pulmonary parenchyma surrounding bronchogenic cysts.[13, 16, 20-24] The question arises whether the lobules of the lung might be the site of elimination of secretions and whether the stage of development of the alveoli is a determining factor in the production of bronchogenic cysts.

In 1910, Pitt[25] suggested that mucus might be removed through the distal part of the pulmonary tree when bronchi are obstructed. Ross[26] has observed that the macrophages and their ingested substances wander back into the alveoli from which they came, when the bronchial tree is obstructed.

On the basis of these observations the following two hypotheses have been formulated: (1) After transection of a bronchus, in the absence of infection, mucus that is normally secreted into the bronchi is phagocytosed in the alveoli.

Abridgment of thesis submitted by Dr. Huppler to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

*Fellow in Surgery, Mayo Foundation.

**Section of Surgery, Mayo Clinic and Mayo Foundation.

***Section of Surgical Research, Mayo Clinic and Mayo Foundation.

(2) If a segment of viable bronchus has both ends closed, a bronchogenic cyst will result from the accumulation of endobronchial mucus. These hypotheses were tested experimentally in 29 dogs.

METHOD

In a control group of dogs the right upper-lobe bronchus was transected and both ends of the divided bronchus were closed by suture (Fig. 1). In these animals, mucus secreted into the right upper-lobe bronchus could not be removed through the trachea by coughing or by movement of the cilia but it could flow into the alveoli.

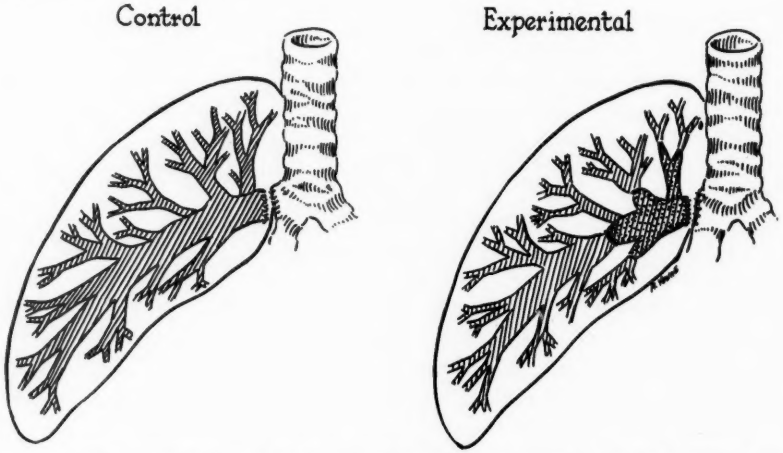


Fig. 1.—Diagram to illustrate the surgical procedures performed. In the control animals, the lobar bronchus was transected and the bronchial stumps were sutured proximally and distally. In the experimental animals, the secondary bronchi were doubly ligated and then the bronchial stumps were sutured. This produced an isolated bronchial segment represented by the cross hatching and stippling.

In the experimental group of animals the right upper-lobe bronchus was transected and the divided ends were closed as in the control animals. In addition, the first four secondary bronchi and the main continuation of the primary bronchus were doubly ligated, thus producing an isolated segment of bronchus. Mucus secreted into this segment could not be removed through the trachea nor could it flow into the alveoli. In the experimental animals the secondary bronchi distal to the isolated segment of bronchus were not ligated; hence, mucus secreted into the bronchus distal to the isolated segment could flow into the alveoli but not into the trachea (see Fig. 1). All of the dogs were given antibiotics for 5 days postoperatively. An animal from each series was killed at varying intervals from 2 to 48 weeks after operation.

RESULTS

The pathologic changes were confined to the right upper lobe. This lobe was small, purplish red, and atelectatic, and the lobes from both groups of animals appeared identical. With one exception, a bronchial cyst was not

produced in the isolated segment of bronchus. The bronchi were dilated an average of two and one-half times the normal diameter and were filled with clear, glary, tenacious mucus (Fig. 2). Measurements of displacement volumes and bronchial diameters did not distinguish specimens of the control group from specimens of the experimental group. From the gross observations it appears that factors other than retention of secretions in an isolated segment of bronchus may be responsible for the formation of bronchogenic cysts.

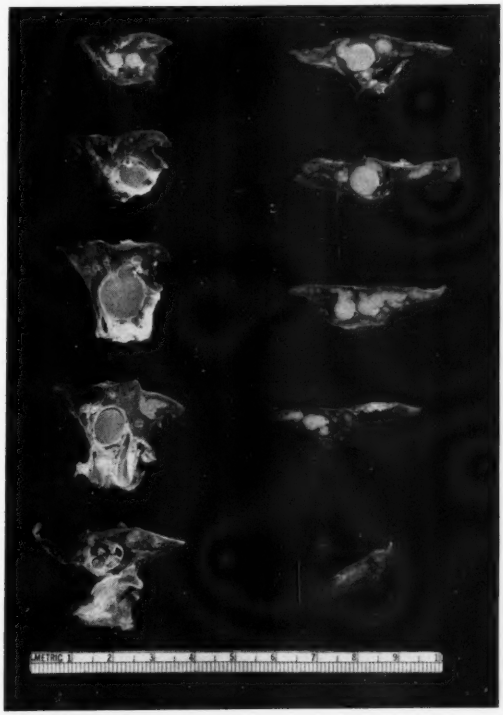


Fig. 2.—Bronchi dilated and full of clear, glary, tenacious mucus. The right upper lobe of the experimental series is indistinguishable grossly from that of the control series.

Blocks of tissue were taken from each specimen through the region of the isolated segment, through the region just distal to the isolated segment and through the tip of the lobe, in both the control and the experimental animals (see Fig. 1). Sections were specially stained to demonstrate mucus. The most significant histologic changes observed were in the alveoli of the region surrounding the isolated segment of bronchus of the experimental animals. Essentially no mucus was present in the respiratory ducts and alveoli and consequently there was no phagocytosis of mucus in the alveoli surrounding the isolated segment of bronchus (Fig. 3). This was as expected because most of the mucus was trapped in the isolated segment of bronchus.

However, mucus was seen in the alveoli of the control animals and also in the alveoli that were distal to the isolated segment of bronchus of the experimental animals (Fig. 4). In the lobules of the lungs of the control animals phagocytes could be seen ingesting mucus within the alveoli (Fig. 5). The terminal bronchi and alveoli did not become cystic, because the secretions were phagocytosed and removed in the lobule of the lung.

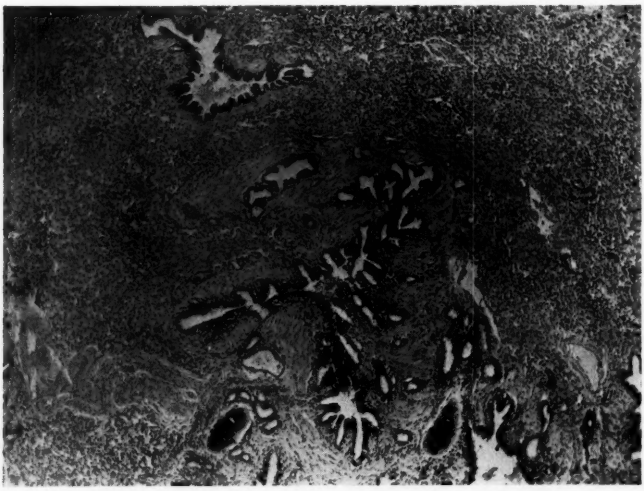


Fig. 3.—Section through pulmonary parenchyma surrounding the isolated segment of bronchus of an experimental animal. There is essentially no mucus in the respiratory ducts and alveoli and consequently no phagocytosis of mucus (mucicarmine; ×50).

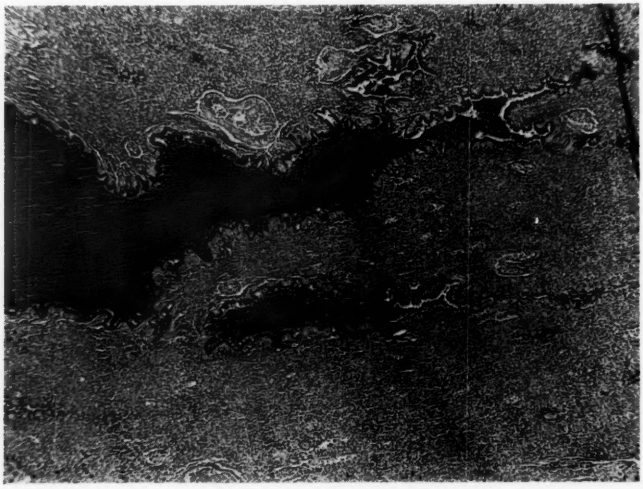


Fig. 4.—Section through pulmonary parenchyma of control animal. Note mucus in bronchioles, respiratory ducts, and a few alveoli (mucicarmine; ×30).

The epithelial lining of the bronchi remained intact, but the ciliated columnar cells underwent metamorphosis and were largely replaced by non-ciliated goblet cells which contained mucus. The mucus within the goblet cells was blended with, and indistinguishable from, the large mass of clear mucus in the bronchial lumen. The bronchial cartilages were widely separated and spaced about the dilated bronchus and there was fragmentation of the elastic fibers of the perichondrium. The tubulo-acinar glands were dilated and mucus was seen within the acini.

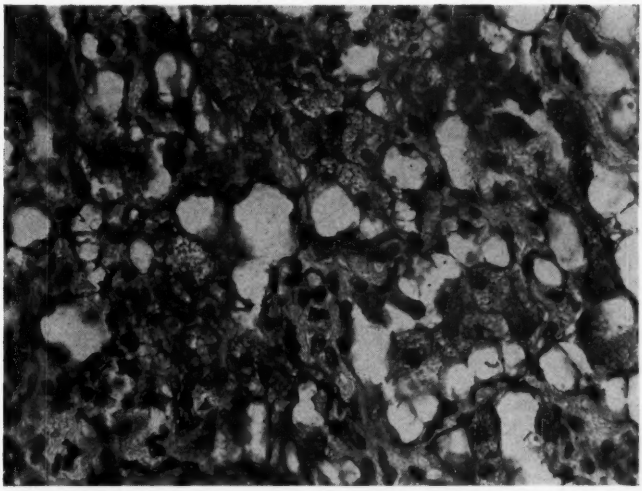


Fig. 5.—Phagocytes ingesting mucus within the alveoli (mucicarmine; ×400).

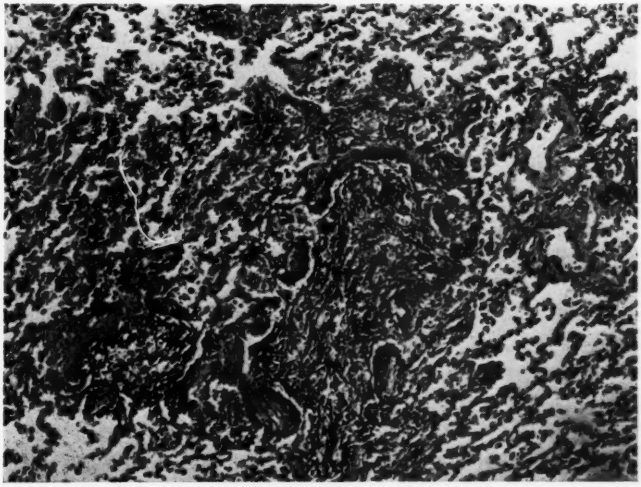


Fig. 6.—Experimental animal killed 44 weeks after operation. Mature fibrous tissue obliterates a bronchiole (hematoxylin and eosin; ×100).

Two weeks after operation, granulation tissue partly occluded the lumina of about 10 per cent of the bronchioles (Fig. 6). Twelve weeks after operation the granulation tissue had been converted into poorly vascularized fibrous tissue which contained moderate amounts of collagen, but this mature granulation tissue did not involve more and more bronchioles.

In animals killed 16 to 48 weeks after operation, the large bronchi remained full of mucus and the epithelium was flattened out. During the same interval there was a decrease in the degree of dilatation of the smaller bronchioles and the respiratory ducts. Fig. 7 shows that the normal convolutions had returned to the bronchiolar epithelium and that the bronchioles were no longer distended with mucus.

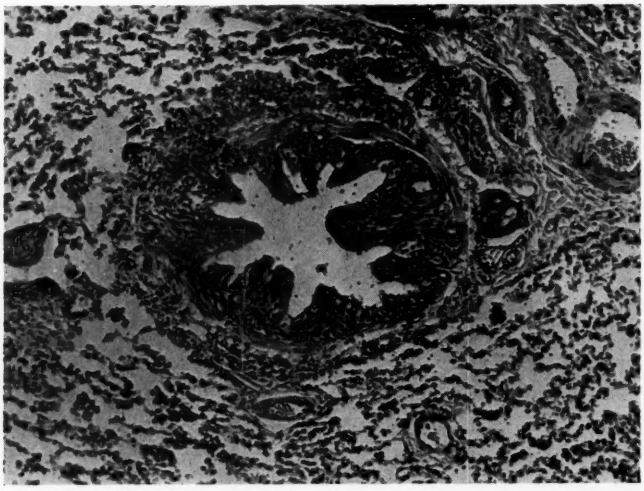


Fig. 7.—Experimental animal killed 42 weeks after operation. The convolutions have returned to the bronchial epithelium and the bronchioles are no longer distended with mucus. Phagocytes in the lobules of the lung have already removed the mucus (mucicarmine; ×100).

COMMENT

These experiments have reaffirmed the many clinical and experimental observations that complete bronchial obstruction *without* infection results in bronchial dilatation by clear mucus.

Essentially the same pathologic condition was produced experimentally by transection of a lobar bronchus as occurs in patients with traumatic rupture of a bronchus. As with traumatic rupture of a bronchus, a mucocele of the lung did not develop, apparently because the secretions that flowed into the lobules of the lung were phagocytosed and carried away.

It has been suggested[18, 19] that cystic bronchiectasis results when mucus dilates the terminal part of the bronchial tree. In these experiments the mucus dilated the terminal part of the bronchial tree, but not cystically. It was at this locus that phagocytes removed mucus, and here the bronchial tree returned

to a normal contour—it did not undergo cystic dilatation. The isolated segment of bronchus is comparable to a bronchogenic cyst that has no connection with the tracheobronchial tree and that also is associated with agenesis of the surrounding alveoli. The isolation of a segment of bronchus approximates the congenital defect postulated by some authors[11-19] to be the cause of bronchogenic cysts. However, with this technique, unequivocal bronchogenic cysts were not produced. One is tempted to speculate that bronchogenic cyst is not the result, but rather the cause, of apparent alveolar agenesis with resulting inability to eliminate secretions by phagocytosis. However, the data and the interpretation of the data obtained from an experimental study such as this are not necessarily explanatory of the disease process in man.

SUMMARY AND CONCLUSIONS

Phagocytosis and removal of mucus were seen histologically in the lobules of the lung when mucus could flow into the respiratory ducts, alveolar ducts, and alveoli. In an experimental group of animals in which the main quantity of secretion was isolated in a bronchial segment, little mucus was present in the lobules of the lung and hence little was available for phagocytosis. In a control group of animals in which the secretions of the respiratory tract could flow into the lobules of the lung, the mucus was phagocytosed and carried away.

It is concluded that, when the tracheobronchial tree is completely occluded in the absence of infection, secretions of the respiratory tract are removed in the lobule of the lung by the process of phagocytosis. When the secretions are retained in an isolated segment of bronchus, a bronchogenic cyst is not produced. The most likely explanation for this—and the one most in accord with present knowledge of the physiology of secreting cells—is that mucous glands and goblet cells secrete until the endobronchial pressure becomes so great that the glands can no longer continue to secrete against the pressure within the bronchial lumen.

REFERENCES

1. Kinsella, T. J., and Johnsrud, L. W.: Traumatic Rupture of the Bronchus, J. THORACIC SURG. **16:** 571-583, 1947.
2. Holinger, P. H., Zoss, A. R., and Johnston, K. C.: Rupture of Bronchus Due to External Chest Trauma; Report of Three Cases With Recovery, Laryngoscope **58:** 817-833, 1948.
3. Paulson, D. L.: Traumatic Bronchial Rupture With Plastic Repair, J. THORACIC SURG. **22:** 636-645, 1951.
4. Paulson, D. L., and Shaw, R. R.: Bronchial Anastomosis and Bronchoplastic Procedures in the Interest of Preservation of Lung Tissue, J. THORACIC SURG. **29:** 238-259, 1955.
5. Thompson, J. V., and Eaton, E. R.: Intrathoracic Rupture of the Trachea and Major Bronchi Due to Crushing Injury, J. THORACIC SURG. **29:** 260-270, 1955.
6. Webb, W. R., and Burford, T. H.: Studies of the Reexpanded Lung After Prolonged Atelectasis, A. M. A. Arch. Surg. **66:** 801-809, 1953.
7. Tannenberg, J., and Pinner, M.: Atelectasis and Bronchiectasis: An Experimental Study Concerning Their Relationship, J. THORACIC SURG. **11:** 571-616, 1942.
8. Cheng, Kwok-Kew: The Experimental Production of Bronchiectasis in Rats, J. Path. & Bact. **67:** 89-98, 1954.
9. Croxatto, O. C., and Lanari, A.: Pathogenesis of Bronchiectasis: Experimental Study and Anatomic Findings, J. THORACIC SURG. **27:** 514-528, 1954.

10. Weinberg, J.: Experimental Production of Bronchiectasis: Study Based Upon Pulmonary Changes Occurring With Bronchial Obstruction, J. THORACIC SURG. **6**: 402-413, 1937.
11. Stoerk, O.: Ueber angeborene blasige Missbildung der Lunge, Wien. klin. Wchnschr. **10**: 25-31, 1897.
12. Swanson, W. W., Platou, E. S., and Sadler, W.: Congenital Cyst of the Lung, Am. J. Dis. Child. **35**: 1024-1031, 1928.
13. Wolman, I. J.: A Case of Congenital Cystic Lung in a Stillborn Fetus, Bull. Ayer Clin. Lab. **2**: 49-54, 1930.
14. Schenck, S. G.: Diagnosis of Congenital Cystic Disease of the Lung, Arch. Int. Med. **60**: 1-21, 1937.
15. Bremer, J. L.: Accessory Bronchi in Embryos: Their Occurrence and Probable Fate, Anat. Rec. **54**: 361-374, 1932.
16. King, J. C., and Harris, L. C.: Congenital Lung Cyst, J. A. M. A. **108**: 274-280, 1937.
17. Klosk, E., Bernstein, A., and Personett, A. E.: Cystic Disease of the Lung, Ann. Int. Med. **24**: 217-232, 1946.
18. Ramsay, B. H.: Mucocele of the Lung Due to Congenital Obstruction of a Segmental Bronchus: A Case Report; Relationship to Congenital Cystic Disease and to Congenital Bronchiectasis, Dis. Chest **24**: 96-103, 1953.
19. Ramsay, B. H., and Byron, F. X.: Mucocele, Congenital Bronchiectasis and Bronchiogenic Cyst, J. THORACIC SURG. **26**: 21-29, 1953.
20. Bruwer, A., Clagett, O. T., and McDonald, J. R.: Anomalous Arteries to the Lung Associated With Congenital Pulmonary Abnormality, J. THORACIC SURG. **19**: 957-972, 1950.
21. Bruwer, A., Clagett, O. T., and McDonald, J. R.: Intralobar Bronchopulmonary Sequestration, M. Clin. North America, July, 1954, pp. 1081-1090.
22. Boyd, G.: Intralobar Pulmonary Sequestration, Dis. Chest **24**: 162-172, 1953.
23. Heuter, C.: Ueber angeborene Bronchiektasien und angeborene Wabenlunge, Beitr. path. Anat. **59**: 520-538, 1914.
24. Willis, F. E. S., and Almeyda, J.: Cystic Disease of the Lung: Broncho-alveolar Cysts, Tubercle **24**: 27-51, 1943.
25. Pitt, G. N.: The Bradshaw Lecture on the Results of Bronchial Obstruction, Brit. M. J. **2**: 1845-1852, 1910.
26. Ross, I. S.: Pulmonary Epithelium and Proliferative Reactions in the Lungs. A Study of the Cellular Response in Lungs After Intratracheal Injection of Toxic and Nontoxic Foreign Substances, Arch. Path. **27**: 478-496, 1939.

SURGICAL TREATMENT OF VENTRICULAR SEPTAL DEFECTS: A METHOD UTILIZING SELECTIVE CORONARY PERFUSION AND HYPOTHERMIA

JOHN B. GROW, M.D., CHARLES V. DEMONG, M.D. (BY INVITATION), AND CHARLES R. HAWES, M.D. (BY INVITATION)
DENVER, COLO.

THE use of hypothermia in the manner suggested by Bigelow and his associates[1] to perform intracardiac surgery under direct vision has proved to be a remarkably valuable and safe method for the closure of interatrial septal defects and for incision of the valve in pulmonary valvular stenosis. Attempts to use this method to produce and repair interventricular septal defects in experimental animals soon disclosed that right ventriculotomy under hypothermia is a hazardous procedure. Ventriculotomy alone under hypothermia with inflow-outflow occlusion of the heart has been shown by many investigators to be complicated by ventricular fibrillation with failure of the experimental animals to survive in an exceedingly high percentage of the experiments. Adding to this the dangers inherent in operating upon the ventricular septum under direct vision, the more important of which are injuries to the conduction system and coronary air embolism, the risk of applying this method to the repair of interventricular septal defects in human beings was made prohibitive. This led to an intensive study of the metabolic changes in the heart muscle responsible for the production of ventricular fibrillation and to the demonstration by Shumway, Gliedman, and Lewis,[2] and others, that perfusion of the coronary arteries with arterialized blood was effective in sharply reducing the incidence of ventricular fibrillation, and that resuscitation was readily accomplished in those instances where it did occur. The demonstration by Shumacher and his associates,[3] of the role played by the autonomic nervous system in the production of ventricular fibrillation together with the effectiveness of sino-auricular node blockade in preventing its occurrence, further decreased the hazards of this complication. Successful results following operations on the right ventricle and interventricular septum in hypothermic dogs, using cardiac occlusion, coronary perfusion, and sino-auricular node blockade, encouraged us to apply this method clinically in selected patients. This paper presents our experience with the use of this method in 10 patients with interventricular septal defects (Table I).

From the Surgical Service, The Childrens Hospital, Denver, Colo.
Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

TABLE I

CASE	AGE (YR.)	PRESSURE MM. HG P.A.	R.V.	RESULT	COMMENT
1.	S.Y. 1½	70/28	60/14	Survived	No murmur
2.	W.S. 30	76/15	74/0	Survived	Much improved; no murmur; working; P.O. catheterization, P.A. 44/14, no shunt
3.	M.L. 34	?	76/0	Died	Ventricular fibrillation 5 minutes following release of occlusion tapes; defibrillation unsuccessful; extreme pulmonary arteriosclerosis
4.	S.H. 4½	60/26	66/0	Survived	Murmur present; doing well
5.	M.H. 6½	118/52	112/0	Survived	Murmur present; P.O. catheterization, P.A. 45/15; no shunt
6.	F.A. 11	63/20	62/2	Survived	Murmur present; weight gain; no dyspnea
7.	L.M. 9	70/24	70/0	Died	Cardiac decompensation due to aortic insufficiency result of distortion by suture; died two months following operation; defect closed
8.	L.M. 8	100/50	100/0	Survived	Murmur present; P_2 decreased; heaving cardiac impulse no longer present
9.	C.O. 6	110/78	124/8	Survived	Murmur present; stormy postoperative course; cardiac failure difficult to control; gradual improvement now
10.	S.M. 10	112/48	106/0	Died	Complete heart block with ineffective rate following release of occluding tapes; defect closed

METHOD

Intratracheal gas-oxygen-ether anesthesia supplemented by hypothermia was used in each case. The body temperature at the time of the occlusion varied from 80° to 83° F.

The technique of coronary artery perfusion was similar to that described by Shumway and his co-workers,[2] and differed only in the method of pumping the blood into the isolated aortic arch. The blood used for perfusion was arterialized venous blood collected into heparin-glucose solution, and was drawn from donors shortly before using and kept at a temperature of 90° F. until the time of perfusion. Umbilical tapes were placed around the following vessels: (Fig. 1) both venae cavae, the innominate artery, the left common carotid artery, the pulmonary artery, and the aortic arch between the left common carotid and the left subclavian arteries. A plastic catheter was placed in the right subclavian artery at the apex of the pleural space and advanced into the ascending aorta. In some cases the catheter was inserted into the left subclavian artery, and in these cases the tape on the aortic arch was placed distal

to the left subclavian artery. The distal end of this catheter was connected to a system of three three-way stopcocks by plastic tubing. The bottles of oxygenated blood were connected to this system of stopcocks by plastic tubing. Two siliconized 20 c.c. glass syringes were also connected to the stopcocks.

After infiltrating the sino-auricular node region with one per cent Novocaine, the tapes on the venae cavae and the aortic arch were tightened and, after allowing time for the heart to empty, the tapes on the pulmonary artery,

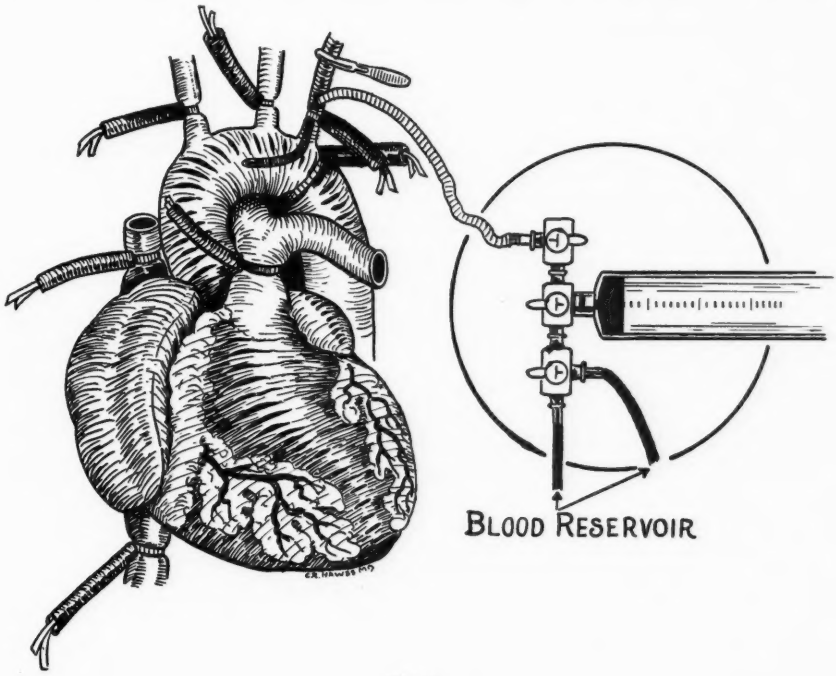


Fig. 1.

innominate artery, and left common carotid artery were tightened. The incision in the right ventricle was made and the coronary artery perfusion begun; the oxygenated blood being alternately pulled from the reservoir into the syringe and injected into the isolated proximal aorta. The rate of perfusion has been approximately 2 c.c. per pound per minute, and even in adult patients has not exceeded 120 c.c. per minute (Table II). The septal defects have been closed using a running or interrupted silk sutures. Ringer's solution was injected into the left ventricular cavity before complete closure of the defect, and into the right ventricle before completely closing the incision in the right ventricle. The occluding tapes on the venae cavae, pulmonary artery, innominate artery, and left common carotid artery were then released. The tape on the aortic arch was not removed until the heart had resumed a strong, effective beat.

TABLE II

CASE AGE (YR.)		OCCLUSION TIME (MIN.)	CORONARY ARTERY PERFUSION (C.C.)	VENTRICULAR FIBRILLATION
1.	S.Y. 1½	14½	493	0
2.	W.S. 30	10	1100	0
3.	M.L.	10	820	Five minutes after release of occlusion tapes; could not be defibrillated
4.	S.H. 3½	9	420	0
5.	M.H. 6½	12	750	0
6.	F.A. 11	8	600	Inadvertent use cold blood for perfusion (76°F.); defibrillated
7.	L.M. 9	10½	740	0
8.	L.M. 8	9½	650	0
9.	C.O. 6	10	500	0
10.	S.M. 12	11	750	0

RESULTS

This method has been employed in 10 patients with interventricular septal defects; 7 of these 10 have survived (see Table I). All 10 patients had symptoms varying from moderate exertional dyspnea and fatigue to repeated episodes of cardiac failure. In all 10 cases, there were loud harsh systolic murmurs along the left sternal border and moderate to marked cardiac enlargement. The second pulmonic sound was accentuated. Electrocardiograms revealed right ventricular hypertrophy and demonstrated diastolic overload patterns in most cases. Cardiac catheterization revealed moderate to marked right ventricular and pulmonary artery hypertension and a left-to-right shunt at the ventricular level. None of the surviving patients has shown evidence of neurological injury. In 2 patients, murmurs are no longer present. All those surviving have shown improvement as evidenced by less dyspnea, a more quiet heart action, decreased intensity of the second pulmonic sound, and less vascular lung fields. Cardiac catheterization four months after operation in cases Nos. 2 and 5 showed no evidence of a shunt and there was a notable decrease in the pulmonary artery pressure.

In 2 cases, excessive postoperative bleeding required a second thoracotomy (Table III). The amount of drainage in the chest bottles following operation in these patients has exceeded the amount one would expect in operations not employing hypothermia, cardiac occlusion, and perfusion. Studies of bleeding and clotting times, prothrombin and prothrombin consumption times, and

TABLE III

CASE	POSTOPERATIVE BLEEDING	DISTURBED CONDUCTION POSTOPERATIVE
1.	0	0
2.	0	Partial RBBB pre- and postoperative
3.	–	–
4.	Chest reopened; internal mammary vessel	Complete RBBB
5.	Chest reopened; diffuse oozing	Complete RBBB
6.	0	0
7.	0	0
8.	0	RBBB pre- and postoperative
9.	0	Complete RBBB
10.	–	Complete heart block (died in operating room)

of fibrinolysin activity of the blood in these cases have been done with no constant abnormality having been noted. Vitamin K_1 oxide has been used empirically in the more recent cases and there seemed to be less drainage in these patients. Complete heart block occurred in one patient following re-establishment of the circulation, and death occurred in the operating room because of the very slow heart rate. Complete right bundle branch block occurred in 3 of the 7 surviving patients.

DISCUSSION

In all of the cases, the heart action during the period of coronary artery perfusion was excellent. There was active bleeding from the small branches of the coronary arteries divided in the line of the ventriculotomy incision, and the myocardium remained a uniformly pink color. Ventricular fibrillation occurred in 2 cases following re-establishment of the circulation (see Table II). In case No. 6, it was possibly related to the perfusion of cold blood. Defibrillation in this patient was readily accomplished. Ventricular fibrillation also occurred in case No. 3 and was irreversible. Post-mortem study in this patient showed the most marked degree of pulmonary arteriolosclerosis that we have seen, and the myocardium contained focal areas of subacute necrosis.

From our limited experience, we feel that the method described effectively prevents coronary air embolism by keeping the aortic valves closed during the period that the ventricles are open, since there were no instances of this complication in the series. Although we seem to be able to eliminate or materially reduce the hazards of ventricular fibrillation and coronary air embolism, the time limits of the procedure do not allow for accurate evaluation of injuries to the conduction system during the placement of sutures and would not allow sufficient time for the placement of a prosthesis should it not be possible to

close the defect by suture methods. In addition, the technical difficulties and very real risk inherent in hypothermia itself must be taken into account. This method was undertaken before effective pump-oxygenators were available. However, we feel that all methods using hypothermia in direct vision cardiac surgery will inevitably be supplanted by the development of a safe, relatively simple, effective pump-oxygenator.

SUMMARY

1. Seven out of 10 patients survived closure of interventricular septal defects employing a method utilizing hypothermia, sino-auricular node blockade, cardiac occlusion, and selective coronary artery perfusion.

2. The method has the disadvantages and hazards of hypothermia itself and, in addition, the time limit imposed by interruption of the cerebral blood supply does not permit unhurried repair of the defect by whatever method seems most suitable in the individual case.

REFERENCES

1. Bigelow, W. G., Callaghan, J. C., and Hopp, J. A.: General Hypothermia for Experimental Intracardiac Surgery, Ann. Surg. **132**: 531, 1950.
2. Shumway, N. E., Gliedman, M. L., and Lewis, F. J.: Coronary Perfusion for Longer Periods of Cardiac Occlusion Under Hypothermia, J. THORACIC SURG. **30**: 598, 1955.
3. Riberi, A., Siderys, H., and Shumacker, H. B.: Ventricular Fibrillation in the Hypothermic State. I. Prevention by Sino-Auricular Node Blockade, Ann. Surg. **143**: 216, 1956.

A REPORT ON HETEROLOGOUS VASCULAR SHUNTS (BOVINE BRACHIOCEPHALIC) IN EXPERIMENTAL AORTIC ARCH RESECTION

RALPH D. ALLEY, M.D., ALLAN STRANAHAN, M.D., WILLIAM H. SEWELL, M.D. (BY INVITATION), HARVEY W. KAUSEL, M.D. (BY INVITATION), CHARLES E. HUGGINS, LIEUTENANT (MC) USNR (BY INVITATION), THOMAS S. REEVE, M.B.B.S. (SYD. AUST.) (BY INVITATION), AND ALAN S. PECK, M.D., C.M.* (BY INVITATION)
ALBANY, N. Y., AND BETHESDA, MD.

SURGICAL resection of the aortic arch poses two major unsolved problems: (a) a practical method for by-passing the aortic arch during the period of occlusion, and (b) a suitable graft for its reconstruction. This report primarily concerns progress in the experimental solution of the first of these problems.

Our experience in the use of a three-limbed plastic shunt constructed of 10 mm. bore Tygon tubing and siliconed glass joints in experimental resection of the dog's aortic arch[1] and its technically successful (but fatal) application in a clinical case[2] have been previously described. An external shunt of similar principle but fashioned of Ivalon sponge[3] and a combination of Ivalon sponge and horse carotid arteries[4] has been used by DeBakey and Cooley in two technically successful resections of the human aortic arch. In the former of these 2 cases, thrombosis was experienced in the innominate artery limb of the shunt.

Although the Tygon shunt was successfully used in experimental resection of the dog's arch by us, the semirigid system proved cumbersome and dominated the operative field. Accordingly, a shunt of more desirable physical properties was sought and a suitable multilimbed heterologous vascular shunt was obtained by taking advantage of the fact that the bovine aortic arch has but one branch, a common brachiocephalic trunk. This vessel and its carotid and subclavian artery branches are fashioned into a multilimbed shunt by oversewing the stump of the brachiocephalic. Experience in the use of this shunt in aortic arch resection attempted in 24 dogs forms the basis of this report. The method for procurement of the shunt vessels and technical improvements in experimental aortic arch resection including the adjunct use of hypotension are also to be described.

From the Department of Surgery, Albany Medical College, Albany, N. Y., and Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md.

Supported by grants from the Heart Association of Albany County, N. Y., and National Heart Institute, U.S.P.H (H-1927).

The opinions and conclusions expressed in this paper are those of the authors and are not to be construed as official or necessarily reflecting those of the Medical Department of the United States Navy.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

*American Trudeau Fellow.

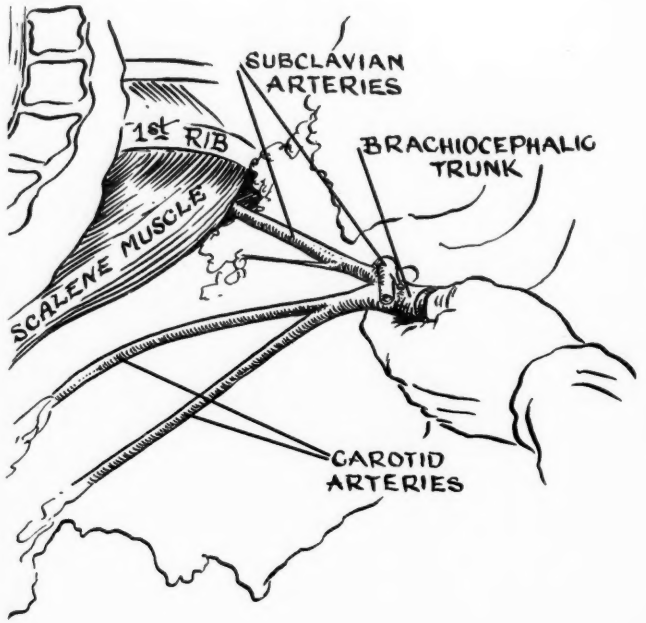


Fig. 1.—Photograph of the inverted left forequarter of a steer showing the method of obtaining subclavian artery branches of adequate length for brachiocephalic shunt purposes. The adjacent line tracing of the pertinent anatomy reveals the relation of the subclavian artery, as it passes into the foreleg, to the angle formed by the anterior border of the scalene muscle and the upper border of the first rib. Incision of the fascia in this angle exposes the subclavian artery which may then be drawn out to the desired length and amputated.

METHODS

Procurement and preparation of the bovine brachiocephalic shunt: The procurement of bovine brachiocephalic vessels with intact carotid and subclavian branches is facilitated by a superficial knowledge of the related anatomy and customary slaughterhouse procedure. The simple technique to be described ensures intact subclavian and carotid branches of adequate length without mutilation of the carcass or otherwise hampering the work of the abattoir. (In our early experience, one of the authors narrowly escaped purchase of four sides of beef for impairing their appearance and salability by excessive axillary dissection in the removal of the subclavian branches.)

In selecting a packing house there are obvious advantages in a small government inspected firm where rapport with the management and the government inspector can be established on a personal basis. Moreover, where available, a kosher slaughterhouse is to be preferred for the reason that the ceremonial killing involves severance of the carotid vessels at the angle of the jaw, thus preserving maximum length of these vessels. In a conventional slaughterhouse the method of bleeding involves the blind insertion of a knife in the suprasternal notch of the stunned animal. Incision of the brachiocephalic artery near its origin is intended by this maneuver, but injury of one or more of the carotid and subclavian branches often occurs, rendering the shunt specimen imperfect.

According the usual packing house procedure, the killed animal is suspended by its Achilles tendons from an overhead track, skinned, eviscerated, and split into halves. This involves four operations: (1) removal of the abdominal viscera, (2) removal of the thoracic viscera, (3) splitting the spine to the ligamentum nuchae with a saw and (4) completion of the spine-splitting and division of the ligamentum nuchae with a cleaver. By requesting the temporary deferment of steps 2 and 4, the surgeon can remove the thoracic viscera with intact shunt vessels without imposing a significant delay in the work of the abattoir. A leisurely dissection of the shunt vessels from the thoracic viscera may then be conducted in an area not being used for routine work.

Familiarity with the following simple anatomic details will facilitate the expeditious removal of the thoracic viscera and the shunt vessels from the suspended carcass (Fig. 1). The bovine brachiocephalic artery trifurcates into two subclavian branches and a short common carotid trunk.* The carotid vessels pose no special problem, but the intrathoracic portion of the subclavian vessels is very short due to the narrow thoracic inlet formed by the ring of the first ribs. The subclavian artery passes out of the thoracic cavity anterior to the first rib and immediately in front of the scalene muscle mass, unentangled by fibers of the brachial plexus which, in the ox, pass through the body of this muscle. A short incision through the fascia anterior to the costal origin of

*The vascular anatomy of the horse is similar, but this animal is usually less readily available as a source for shunt vessels.

the scalene muscle permits a finger to be hooked about the subclavian artery which can then be drawn out of the foreleg for an adequate length and amputated, without the necessity of an axillary dissection for its removal.

After the shunt vessels have been dissected free of the thoracic viscera, the shunt is fashioned by oversewing the amputated stump of the brachiocephalic artery, converting it into a manifold for the carotid and subclavian

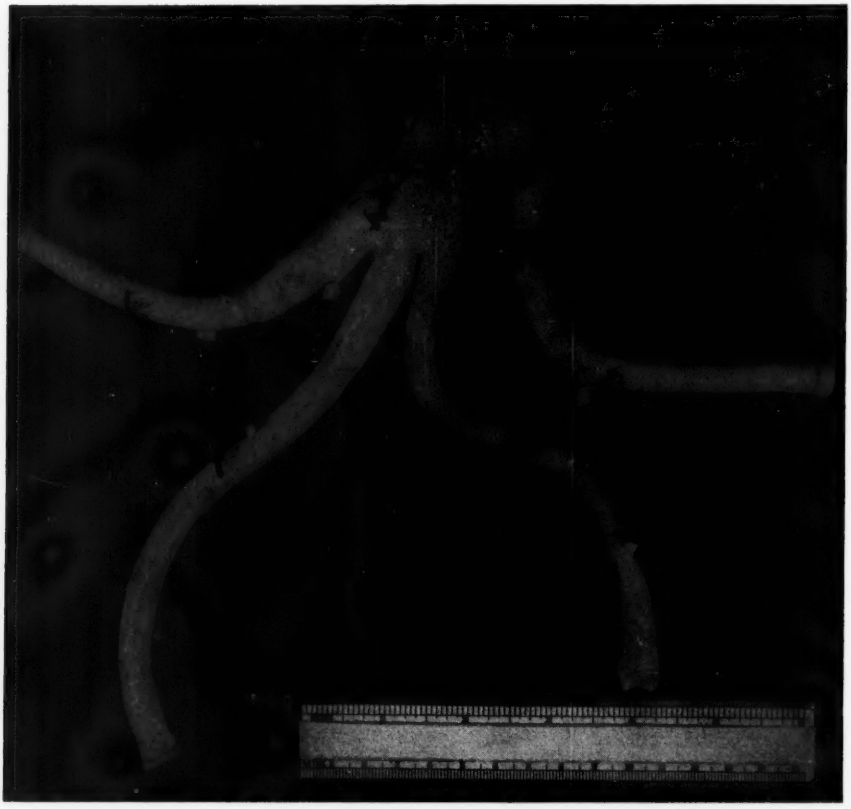


Fig. 2.—A typical bovine brachiocephalic shunt with two carotid and two subclavian artery limbs taken from a 1,000 pound steer is shown. The shunt was fashioned by oversewing the brachiocephalic artery stump as a manifold for the limbs, and all undesirable side branches were ligated and amputated. The shunt is shown in its undistended state.

artery limbs. All undesirable side branches are ligated at their origin and amputated (Fig 2). The average distended diameter and length of the shunt limbs obtained from a 1,000 to 1,200 pound steer are as follows: subclavian artery—16 by 190 mm., and carotid artery—16 by 260 mm.

For experimental purposes the prepared shunts are preserved in the frozen state and a nominal effort at gross decontamination is made by soaking

in aqueous Zephiran solution for three hours prior to use. For clinical purposes any of the accepted methods of sterilization and preservation now employed for homografts would be desirable.

Experimental aortic arch resection employing a bovine brachiocephalic shunt and selective hypotension: Adult mongrel dogs were anesthetized with intravenous Nembutal and 100 per cent oxygen administered under intermittent positive pressure through an endotracheal tube. Cannulae inserted into the right femoral artery and vein served for continuous recording of blood pressure by mercury manometer and intravenous drug and fluid administration, respectively. The thorax was entered through the bed of the excised left third rib with the dog in the lateral position, and adequate exposure obtained by fracture of the adjacent fourth rib through its neck. The aortic arch and branches were mobilized and the first two or three pairs of intercostal arteries divided.

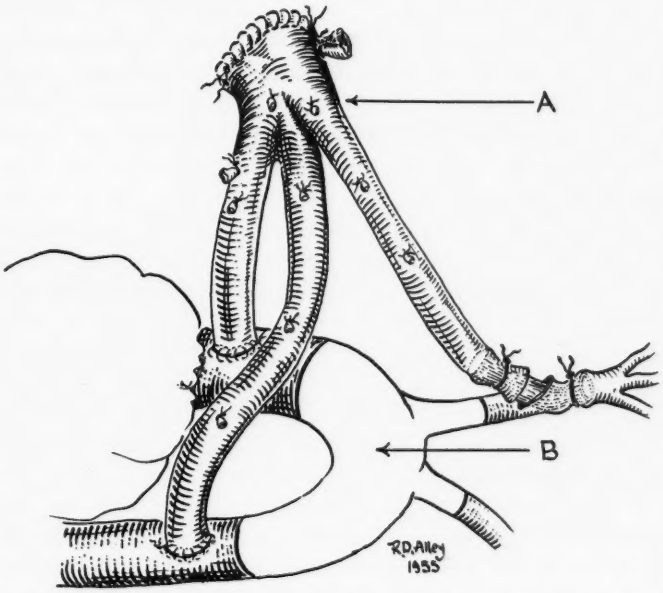


Fig. 3.—*A*, Semidiagrammatic representation of a three-limbed bovine brachiocephalic shunt as supplied in experimental aortic arch resection in the dog. The proximal and distal aortic limbs of the shunt are anastomosed to the host vessel by exclusion clamp technique. The dog's brachiocephalic artery is cannulated by the cephalic limb of the shunt. *B*, Area of dog's aortic arch and branches to be resected and replaced by graft.

The aortic arch was then by-passed by means of a three-limbed bovine brachiocephalic shunt, in the manner depicted in Fig. 3. With the blood diverted through the shunt the arch was excised and replaced by a graft. Freeze-dried, ethylene oxide-sterilized homografts or Ivalon sponge prostheses were used to reconstruct the arch except in one instance wherein a formic-acid treated braided nylon graft was employed.

Arfonad*-induced hypotension was employed during selected steps of the procedure because of the tendency demonstrated in our previously reported series for the proximal aortic shunt anastomosis to disrupt under normal or elevated blood pressures. It is our impression that three factors are responsible for the tendency of disruption at this site:

1. The well-known extreme friability of the ascending portion of the dog's aorta.[5] (An appreciation of the degree of friability of this area can be easily obtained by fracturing the removed specimen transversely with a thumb nail. The longitudinal "grain" splits less readily.)

2. The longitudinal stretch of a portion of vessel contained in a tangential exclusion clamp is a function of the blood pressure present within the vessel when the clamp was applied. This longitudinal tension encourages minute transverse tears at suture line needle puncture sites in the host aorta, thereby weakening the anastomosis.

3. Hypertension induced by the carotid reflex when the dog's brachiocephalic is occluded for insertion or removal of the shunt cephalic limb cannula.

The second and third of these factors can be minimized by inducing hypotension at appropriate times during the procedure as will be described.

Experience has shown that the procedure is best done in the following steps:

1. Mobilization of the arch.

2. Anastomosis of the descending aortic limb of the shunt employing a tangential exclusion clamp technique. The pleura which closely invests the presenting aspect of the descending thoracic aorta is preserved to strengthen the suture line.

3. The systolic blood pressure is then depressed by intravenous administration of a solution of Arfonad containing 0.5 mg. per cubic centimeter until it has fallen to 85 mm. Hg. Experience has shown that the administration of 5 drops or less of the Arfonad solution at a time will safely depress the blood pressure to the desired level without overshooting the mark. As a precaution, however, a solution of Levophed† bitartrate containing .004 mg. per cubic centimeter is kept available as an antagonist for Arfonad overdosage. With the blood pressure at the depressed level, the proximal limb of the shunt is anastomosed to the ascending aorta and the brachiocephalic artery cannulated with the third limb of the shunt. Air is removed from the shunt system by retrograde filling of the proximal and distal aortic shunt limbs first, and then from the cephalic limb in a similar manner, evacuating the air by hypodermic needle. With the shunt in operation the blood pressure is permitted to drift back to normal.

4. The portion of the arch between the shunt limbs and the left subclavian artery are then occluded, the arch excised, and the graft sutured in place.

*Arfonad—supplied by Hoffmann-La Roche, Inc.
†Levophed—supplied by Winthrop-Stearns.

5. The shunt limbs are then removed in reverse order of their attachment employing Arfonad-induced hypotension to 85 mm. Hg systolic during the removal of the ascending aortic and cephalic limbs.

RESULTS

The aortic arch was by-passed by means of this technique in 24 dogs. The period during which the shunt was in actual operation varied from one to five hours. (The longest period was occasioned by the necessity of the operating surgeon to interrupt reconstruction of the arch to conduct a clinic.) The arch successfully resected and replaced by a graft in 19 of these animals.

The elastic properties of the shunt proved to be a great asset in that the shunt limbs could be retracted out of the way to facilitate exposure without threat of kinking. Indeed, with shunt limbs of adequate length the manifold could be permitted to rest on the dog's chest wall in any portion of the periphery of the wound. The pulsation of the shunt was striking and arouses the speculation that the diastolic "systole" of the large shunt manifold may promote coronary filling.

Adequacy of blood flow through the shunt was inferred grossly by an absence of demonstrable difference in right femoral artery pressure as measured by mercury manometer in the blood delivered by the shunt alone and by the dog's aortic arch with the shunt excluded.

Among the 19 dogs surviving operation, only one demonstrated central nervous system damage. This animal differed from the rest in that during the occlusion of the dog's brachiocephalic artery for removal of the cephalic limb of the shunt, the left subclavian artery was inadvertently left occluded, thereby depriving the brain of aortic arch circulation for a period of ten minutes. The dog never regained consciousness and died seven days later. Unfortunately, the brain was not examined at autopsy.

In all but one instance the shunt remained free of thrombi. During this procedure a succession of technical errors with attendant excessive loss of blood led to a prolonged period of profound hypotension ending in death. All limbs of the shunt were found occluded by thrombus. The shunt employed, however, had been thawed on two separate days and prolonged exposure to room temperature may have induced deleterious changes in its intimal lining which predisposed to thrombosis during hypotension. The other four operative deaths were due to technical factors unrelated to the shunt as follows: rupture of the host aorta proximal to the shunt due to exclusion clamp fracture of its wall, respirator failure, inadvertent obstruction of the pulmonary artery by traction, and hemorrhagic shock. No dogs were lost due to hemorrhage at the shunt implantation sites.

A detailed report on the fate of the dogs surviving operation will form the basis for part of a separate study devoted to the behavior of aortic arch grafts. In brief, however, 10 of the 19 operative survivors died within the first postoperative day, 5 lived periods varying from three days to five and one-half weeks, and 4 are living and well five and one-half weeks, six weeks, eleven

months, and one year postoperatively, respectively. (The sole long-term survivor of aortic arch resection with homografting of our first series is doing well two and one-half years postoperatively.)

DISCUSSION

The operative mortality in this series of experimental aortic arch resections employing an heterologous vascular shunt in the dog is 20.8 per cent compared with 55.5 per cent in the previously reported series employing a Tygon shunt. Some of the improvement is due to increasing experience as evidenced by the fact that the more experienced team had a mortality of only 10 per cent in the present series.

Five operative deaths in the previous series were due to disruption at the site of the proximal shunt limb implantation on the ascending aorta. The absence of this occurrence in the present series is ascribed to the use of hypotension during certain steps of the procedure, and to a lesser degree to the use of a shunt with elastic properties.

Experience in this series of aortic arch resections has demonstrated the bovine brachiocephalic shunt technique to have the following desirable features: (1) the material is readily available and can be preserved by homograft preservation methods; (2) having the same elastic properties of the vessel it temporarily surplants, there is negligible interference with hemodynamics; (3) its elastic properties and long limbs provide mobility thereby facilitating exposure for grafting; (4) the lining of the shunt is essentially nonthrombogenic if being actively perfused by blood; and (5) the shunt is applied to the aorta employing standard vascular surgical techniques, without the hazard of the critical dexterous maneuver demanded by mechanical coupling methods.[6, 7]

The unhampered exposure permitted by the mobility of the brachiocephalic shunt is an asset not shared by the shunt-graft technique successfully employed experimentally by Satinsky and his co-workers.[8] Bailey's[9] effort to employ this method in a clinical case of large aortic arch aneurysm was largely frustrated by exposure problems imposed by the usual adherence of the pathology to surrounding structures and the presence of the shunt-graft in the field of dissection. The bovine brachiocephalic shunt would appear more promising of practical application in the clinical case.

It is hoped that the detailed description of the method of bovine brachiocephalic shunt procurement and its use in experimental resection of the dog's aortic arch will stimulate others to employ the method in the experimental evaluation of homografts and the various prosthetic materials in the aortic arch location. It might be added that this technique of aortic arch resection involves six separate and different anastomoses and three vascular suture lines which constitute a valuable training excercise for residents interested in vascular surgery.

The authors would like to express their appreciation to Mr. Robert Replogle for skilled technical assistance. We are indebted to the Department of Medical Illustration, Veterans Administration Hospital, Albany, N. Y., for preparation of illustrative material, including the motion picture shown at the Thoracic Surgical Forum.

REFERENCES

1. Alley, R. D., Sewell, W. H., Formel, P. F., Stranahan, A., Kausel, H. W., and Koth, D. R.: Experimental Evaluation of External Shunts for By-Passing the Thoracic Aorta, Surg. Forum, Am. Coll. Surgeons, W. B. Saunders Co.. Philadelphia **5**: 85, 1954.
2. Stranahan, A., Alley, R. D., Sewell, W. H., and Kausel, H. W.: Aortic Arch Resection and Grafting for Aneurysm Employing an External Shunt, J. THORACIC SURG. **29**: 54, 1955.
3. Cooley, D. A., Mahaffey, D. E., and DeBakey, M. E.: Total Excision of the Aortic Arch for Aneurysm, Surg., Gynec. and Obst. **101**: 667, 1955.
4. DeBakey, M. E., et al.: To be published in Surgery.
5. Carrel, A.: Report on the Experimental Surgery of the Thoracic Aorta and Heart, Ann. Surg. **52**: 83, 1910.
6. Izant, R. J., Hubay, C. A., and Holden, W. D.: A Non-Suture Aortic Shunt—Experimental Study, Surgery **33**: 233, 1953.
7. Fryfogle, J. D., Small, J. T., Stenborg, W., and Samberg, C.: Rapid Vessel Anastomosis With Transient Arterial Interruption Employing Suture Methods Over a Removable Bivalve Prosthesis. Henry Ford Hospital International Symposium on Cardiovascular Surgery, Philadelphia, 1955, W. B. Saunders Co., p. 476.
8. Satinsky, V. P., Neptune, W. B., and Alai, J.: Experimental Transplantation of the Complete Arch of the Aorta, Ann. Surg. **141**: 38, 1955.
9. Bailey, C. P.: Surgery of the Heart, Philadelphia, 1955, Lea & Febiger, p. 1033.

AORTIC HOMOGRAFT SUBSTITUTION AND BY-PASS IN SUPERIOR VENA CAVAL OBSTRUCTION

JOHN F. HIGGINSON, M.D.
PORTLAND, ORE.

THE clinical picture of superior vena caval obstruction has been well depicted and discussed in previous articles and discussions in the literature. Many of these, especially the more recent, have been by members of this Association, who have amply referred to articles preceding their own, so that repeated reference is unnecessary except for purposes of pointed discussion.

At the 1954 meeting in Montreal, Scannell and Shaw[1] presented a paper on the relief of superior vena caval obstruction by the use of free vein grafts. We agree with their statement that most cases of superior vena caval obstruction are the result of inoperable malignancy, and we believe now with others that perhaps a number of these can be afforded relief by palliative by-pass, in addition to the use of x-ray therapy. We agree that benign processes causing superior vena caval obstruction should be considered for surgical correction by means of reconstruction of the superior vena cava.

We have had occasion recently to treat one case of benign obstruction of the superior vena cava by resection of the innominate veins and superior vena cava with substitution of an aortic-iliac bifurcation homograft, and to treat 2 cases of malignant obstruction of the superior vena cava by establishing an aortic homograft shunt between the left innominate vein and the right auricular appendage.

CASE REPORTS

CASE 1.—The patient was a 28-year-old man first admitted to Veterans Administration Hospital, Portland, Oregon, on May 12, 1955, with obvious superior vena caval obstruction of two months' duration. He had had a negative survey chest x-ray eight months previously. Blood pressure was 148/90 mm. Hg. Venous pressure was 28 cm. of water. Chest x-rays showed a 3 cm. rounded mass in the right superior hilar area. Angiocardiograms showed constriction of the superior vena cava at its point of origin. Intermediate purified protein derivative was positive and histoplasmin was 4 plus.

On May 24, 1955, the patient was explored via a right posterolateral thoracotomy. The medial aspect of the right upper lobe had to be sharply dissected off a bulging, firm, fixed mass found cephalad to the hilus and anterior to the trachea and encasing the right phrenic nerve and superior vena cava and distal azygos vein and distal innominate veins. The phrenic nerve was dissected free. Biopsies and frozen section "suggested a neurogenic tumor." Following pericardiotomy, about 1 to 1.5 cm. of distal superior vena cava was found uninvolved. The proximal ends of both innominate veins were found uninvolved.

From the surgical services of the Good Samaritan and Veterans Administration Hospitals, Portland, Ore.

Reviewed in the *Veterans Administration* and published with the approval of the Chief Medical Director. The statements and conclusions published by the author are the result of his study and do not necessarily reflect the opinion or the policy of the Veterans Administration.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

As the mass was sharply dissected off the trachea the posterior portion of the mass was found to be old calcific, granulomatous, and anthracotic lymph node material. An aortic-iliac bifurcation homograft (frozen dried) was then placed upside down as the mass was removed with encased distal innominate veins and proximal superior vena cava. The proximal right innominate vein was anastomosed first to one iliac limb of the homograft, and then the proximal left innominate vein and the distal superior vena cava were clamped and divided and the specimen was removed. The aortic end of the homograft was then anastomosed to the distal superior vena cava stump, the homograft was filled with a dilute heparin solution, the other iliac limb was clamped, and venous return re-established via the right innominate vein and homograft and superior vena cava stump. The third anastomosis was then done. There was immediate improvement on the table of the patient's cyanosis and edema. Postoperative venous pressure was 15 cm. water.

Postoperative angiogram was done two months after operation, but unfortunately only via the left arm. Patency was demonstrated on the left side, and although the patient was clinically fine, the angiogram suggested some narrowing of the lumen of the homograft. Bilateral simultaneous angiograms were done eleven months postoperatively on March 30, 1956, and these demonstrated patency of the graft and perhaps a slight increase in the narrowing of the lumen of the homograft. His venous pressure was 18 cm. of water and he was clinically well. The specimen proved to be a "nonspecific granuloma" densely involving the proximal superior vena cava and distal innominate veins. Because of the impression of the pathologist at the time of frozen section, no portion of the specimen was saved for cultural study or animal inoculation, which might possibly have established a definite etiology.

CASE 2.—A man, 53 years old, was a private patient first seen Nov. 3, 1955, with a two weeks' established superior vena caval obstruction preceded by six months of cough. He was having attacks of syncope, and had to sleep upright in a chair. His face, neck, and upper trunk and arms were dusky, suffused, and swollen. There was a wheeze in the right upper chest. X-rays showed a right superior mediastinal mass. Bronchoscopy and aspirate were negative except for evidence of extraluminal tracheal compression. Scalene lymph node biopsy was negative. Left arm angiograms demonstrated complete obstruction of the superior vena cava and probable obstruction of the right innominate vein.

The undiagnosed tumor was explored through a midline sternotomy on Nov. 11, 1955. Involving the pretracheal and paratracheal areas was found a large mass to which the medial aspect of the right lung was densely adherent. The azygos vein was buried in the mass and the superior vena cava was grossly involved by the tumor with extension into the right atrial wall. No separate tumor could be felt in the right lung, but the medial aspect of the right upper lobe was part of the mass just described and a primary bronchogenic carcinoma was suspected. Biopsy of one of the matted confluent lymph nodes showed metastatic carcinoma.

A reconstituted frozen dried aortic homograft was anastomosed to the right auricular appendage following partial amputation. Upon incising the left innominate vein, a thrombus was found in it but with release of the proximal vein the blood flow pushed the firm thrombus out and the homograft was then anastomosed to the side of the left innominate vein. The right innominate vein was proved to be obstructed by tumor involvement proximally.

Immediate satisfactory flow ensued upon removing the clamps and the patient's venous pressure was immediately altered, although the right arm did not immediately improve as much as the left, for the reason just mentioned. The patient was given deep x-ray therapy postoperatively and did very well. He was delighted to be rid of the superior vena caval obstruction and the change objectively was very striking. He was last seen on Feb. 14, 1956 (three months after operation), and was clinically still free of superior vena caval obstruction except for slight prominence of the veins of the right upper chest wall. He was, however, beginning to have some low back pain suggesting metastasis. Recheck x-rays of Feb. 10, 1956, showed some slight decrease in the size of the tumor.

Fig. 1.—Case 2. Aortic homograft shunt—four and one-half months in situ. Graft is wrinkled and irregularly contracted, and there is gross evidence of calcification.

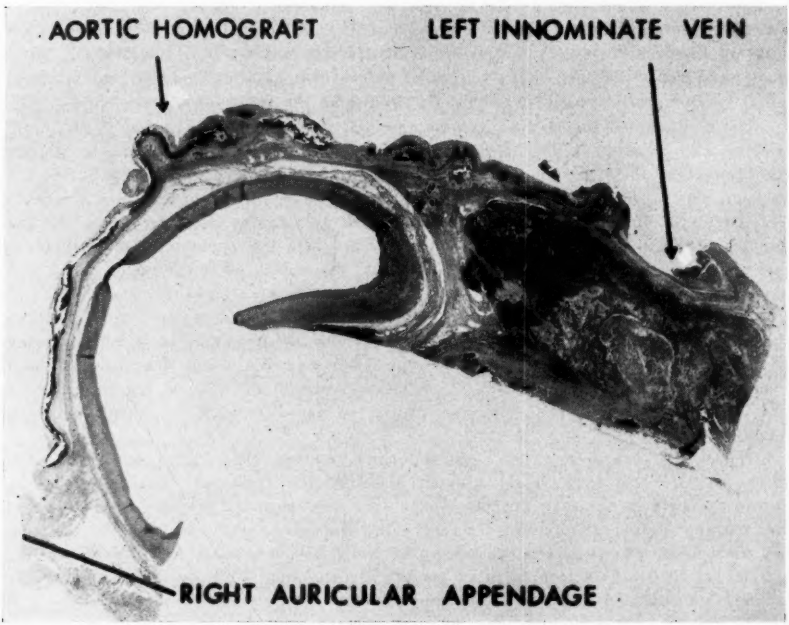


Fig. 2.—Case 2. Calcification in areas of necrosis occurring subintimally and in adjacent media. Thickening of intima by edema and actual fibrous tissue. Condensation and decrease of elastic tissue of media. Patient's own aorta included in this mounted microscopic section.

During the second week in March, 1956, the patient began to fail rapidly, and during this time his home-town doctor noted some slight transient congestion of the patient's face.

He died on March 24, 1956, four and one-half months after operation. Autopsy showed extensive widespread carcinomatosis. The primary tumor, as suspected, was in the medial portion of the right upper lobe, immediately contiguous to the azygos vein and superior vena cava. The superior vena cava and right innominate vein were plugged by tumor. The left innominate vein, homograft, and right auricular appendage were patent, but there had been a striking change in the homograft (Fig. 1). Its wall was wrinkled, sclerotic, contracted, and there were subintimal calcific plaques in it (Fig. 2). Proximally there was a thin veil of mural thrombus. The calcification was in areas of necrosis which had occurred subintimally and in the adjacent portion of the media. The elastic tissue of the media was condensed and decreased as evidenced by elastic tissue stains. The intima was thickened by fibrocellular proliferation. These changes have been described previously by many authors.[2-4] One must consider the possibility that if this man had lived sufficiently long the changes in the homograft might have eventually resulted in obstruction to blood flow.

CASE 3.—The patient was a white man who, at age 23 while in the army, had a fibrosarcoma removed from the soft tissues of the right thigh. Three years later, in August, 1948, a small lump was noted in the right groin and he complained of a slight cough. Bilateral resection of the lymph nodes of the groins revealed no evidence of tumor. Chest x-ray showed six metastatic coin lesions in the right lung field. The left side was clear. At this time, I saw the patient and performed a right pneumonectomy on Aug. 24, 1948. The patient was followed at regular intervals during the next six and one-half years by the Tumor Board of the Veterans Administration Hospital, Portland.

On April 14, 1955, the patient was rechecked and found well except for very slight narrowing of the esophagus on barium swallow. There were no symptoms. Five days later the patient was readmitted because of swelling of the face and hoarseness. There was obvious superior vena caval obstruction and the venous pressure was 31 cm. of water. The vocal cords were not paralyzed. He was discharged by the Tumor Board, but returned in May, 1955, because of increase in symptoms and distress. An angiogram showed what was interpreted as an intrinsic lesion in the superior vena cava at its point of insertion into the right atrium. Venous pressure was 30 cm. of water.

On May 17, 1955, the right chest was explored with the hope of resecting and reanastomosing the superior vena cava. A tremendously thick, tough, solid mass of tissue was encountered. This was largely fibrous tissue on the pleural aspect, and absolutely no sign of cardiac or other mediastinal motion was evident. Dissection at various peripheral points failed to identify a pericardial cavity, but masses of tumor were found and identified as recurrent low grade fibrosarcoma. While dissecting posteriorly and laterally in the region of the right atrium, a small hole was made in what seemed to be a heavy layer of tissue, and through this opening there appeared a pulsing flow of tumor tissue and fresh blood clot. It could not be ascertained whether we had opened into a tumor-and-blood-filled posterior pericardial sac or into a tumor-invaded right atrium, and this hole and then the patient's chest were closed.

Surprisingly, the patient's superior vena caval obstruction improved considerably from this exploration, probably due to some degree of decompression, and this has been offered in the past as a form of surgical treatment.[5]

By September, 1955, the Tumor Board reported that clinically the superior vena caval obstruction had disappeared, but no venous pressure was recorded.

He was readmitted on Oct. 26, 1955, for consideration of a by-pass procedure. The obstruction had recurred and angiography on Nov. 23, 1955, showed a patent left innominate vein with almost complete obstruction of the superior vena cava. On Nov. 29, 1955, the sternum was split and a shunt was established between the right auricular appendage and the side of the left innominate vein by means of an aortic homograft. Complete relief of the superior vena caval obstruction was obtained.

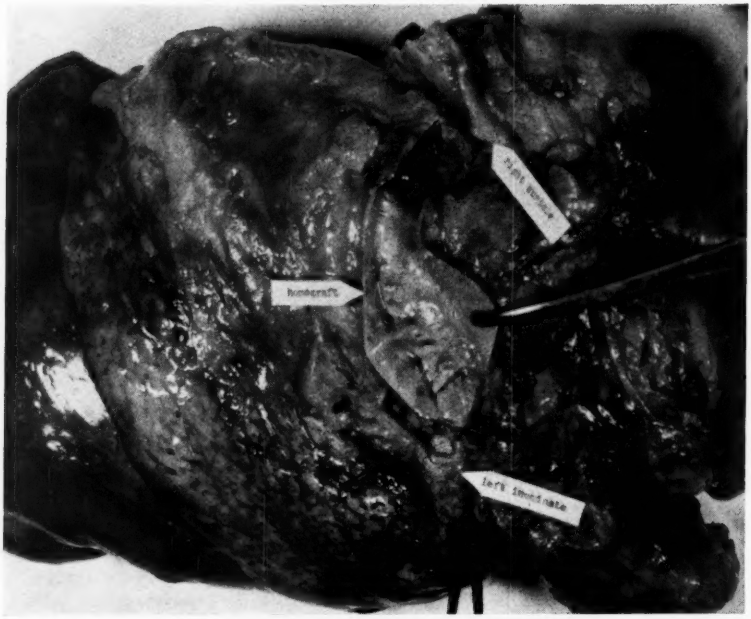


Fig. 3.—Case 3. Aortic homograft shunt—six weeks in situ. Wrinkling of graft grossly.

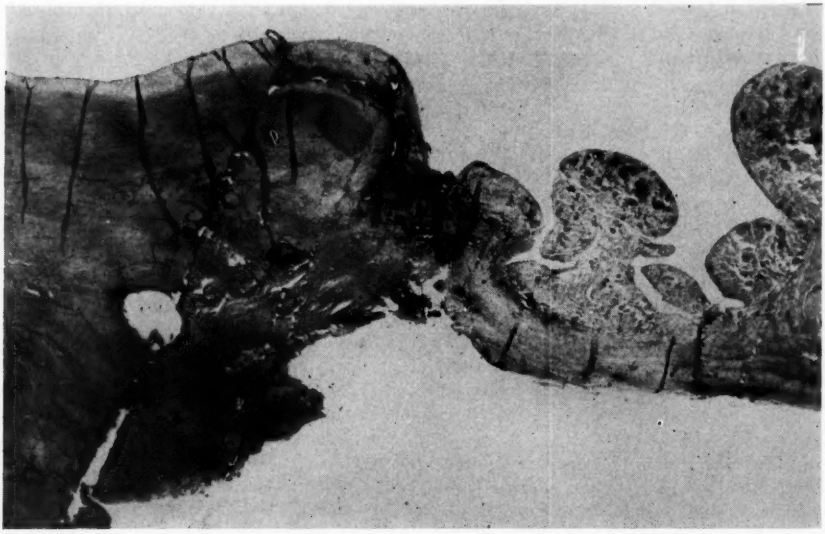


Fig. 4.—Case 3. Aortic homograft—six weeks in situ. No detectable change microscopically except very slight proliferation of fibrous tissue along intima of graft from anastomosis. Graft to left. Auricular appendage on right.

He did well until January, 1956, when he developed dyspnea and a cough. Basal râles were noted in the remaining lung. He began to have recurrence of his superior vena caval obstruction syndrome and venous pressure on Jan. 10, 1956, was 34 cm. of water. It was thought that the homograft had probably thrombosed, but angiography on Jan. 12, 1956, showed the homograft to be patent.

The patient died on Jan. 14, 1956 (six weeks after the shunt operation), and autopsy showed the innominate vein, homograft, and right auricular appendage to be patent without any evidence of thrombosis (Fig. 3).

However, the operative findings of May, 1955, the terminal dyspnea, cough, and râles, and the terminal superior vena caval obstruction syndrome were explained by the finding of huge masses of tumor and old and new blood clot in the posterior pericardial sac, compressing the atria and apparently causing an effectual tamponade with obstruction to blood flow.

The aortic homograft grossly showed some wrinkling, but microscopically it could not be distinguished from a normal aorta even by means of various stains (Fig. 4), but there was some beginning proliferation of fibrous tissue along the intima of the graft from the points of anastomosis.

DISCUSSION

The use of aortic homografts as substitutes and shunts in the treatment of arterial disease is well established. Their continued use in the treatment of superior vena caval obstruction merits consideration and further trial. The discussion of Scannell and Shaw's paper[1] by Samson, O'Neill, Kay, Hanlon, Klassen, Deterling, Gerbode, and Holman, covered the various arguments for and against the use of aortic and venous homografts and autografts. It may be that homologous tissues will eventually fibrose or thrombose as Gerbode and Klassen have stated, and the pathologic findings in one and the angiographic findings in another of my cases also suggest this is the fate of these tissues. However, Kay's experience would seem to indicate that venous tissues, whether homologous or autogenous, will also fibrose. This would seem to leave only autogenous aortic grafts as the hypothetically ideal tissue, and these are not readily available.

Insofar as blood vessel replacements generally are concerned, Linton[6] states that homologous arterial grafts thrombose less than other types of grafts, when used in the treatment of arterial disease. Of course this thought may not be equally applicable to veins, perhaps for the reason mentioned by Gerbode,[1, 2] but Hanlon's,[1] Deterling's,[1] and Holman's[1, 7] experiences with aortic homografts in the treatment of superior vena caval obstruction were favorable, and more recently Reveno, Reynolds, and Dodrill[8] have reported the satisfactory use of an aortic homograft for occlusion of both innominate veins, the patient being well fourteen months after operation.

Our own experience recorded here is obviously limited, and the longest follow-up is only eleven and one-half months. Moreover, definite gross and microscopic pathologic changes occurred in one homograft in place for four and one-half months, and we do not know what the ultimate fate will be of the aortic-iliac bifurcation homograft. Nonetheless, our experience has impressed us sufficiently to feel that we should offer this treatment whenever possible, especially as palliation in cases of malignancy. The relief of symptoms is dramatic and striking and is gratefully appreciated by the patient.

It is quite probable that some of the newer plastic materials will prove better and more adaptable and perhaps suffer no changes within the host, but we feel at present that aortic homografts are the best available material for use in the surgical treatment of superior vena caval obstruction either by resection and substitution, or by shunt.

The author wishes to acknowledge gratefully the cooperation and help received by him from D. Altman and B. Stuart, photographers at VAH, Portland, Ore.; to Dr. W. Haug, pathologist at VAH, Portland; and to Dr. M. Heineman and Dr. W. Lehman, pathologists at Good Samaritan Hospital, Portland, Ore.

REFERENCES

1. Scannell, J. G., and Shaw, R. S.: Surgical Reconstruction of the Superior Vena Cava, J. THORACIC SURG. **28**: 163, 1954.
2. Parsons, H. G., Gerbode, F., and Cox, A. J.: Studies in Aortic Autografts and Homografts, Angiology **3**: 306, 1952.
3. Swan, H., Robertson, H. T., and Johnson, M. E.: Arterial Homografts—I. The Fate of Preserved Aortic Grafts in the Dog, Surg., Gynec. & Obst. **90**: 568, 1950.
4. Eade, G. E., Fletcher, T. L., Schlosser, R. J., Zech, R. K., and Harkins, H. N.: Chemical Modification of Arterial Homografts, Surgery **39**: 515, 1956.
5. Gray, H. K., and Skinner, I. C.: Constrictive Occlusion of the Superior Vena Cava, Surg., Gynec. & Obst. **72**: 923, 1941.
6. Linton, R. S.: Some Practical Considerations in the Surgery of Blood Vessel Grafts, Surgery **38**: 817, 1955.
7. Holman, C. W., and Steinberg, I.: Treatment of Superior Vena Caval Occlusion by Arterial Graft, J. A. M. A. **155**: 1403, 1954.
8. Reveno, W. S., Reynolds, L., and Dodrill, F. D.: Occlusion of Both Innominate Veins; Restoration of Blood Flow by Arterial Graft, J. A. M. A. **159**: 1192, 1955.

EXPERIMENTS WITH SUBSTITUTE ESOPHAGUS

LAURENCE H. RUBENSTEIN, M.D.* (BY INVITATION)
CHICAGO, ILL.

IN THE surgical treatment of esophageal lesions, many occasions occur in which it would be a great advantage to be able to replace easily the diseased portion of the esophagus. In a previous report from our laboratory we described the use of autogenous skin transplants as replacements for portions of esophagus.[1] Many subsequent experiments have been conducted and it seems proper now to report our results.

METHODS

The experiments were all carried out on mongrel dogs.

A. Esophageal transplants with preserved and fresh heterologous homografts: A series of experiments in which segments of thoracic esophagus were resected and replaced by grafts of free donor esophagus from another animal led to the same constant results; namely, failure of new graft to "take" and bridge the defect. One hundred per cent failure was due to lack of healing between the normal esophagus and donor graft esophagus with subsequent leakage and empyema.

B. Skin tube grafts: These series of experiments were previously reported in the Fundamental Forum of The American College of Surgeons (1952). We concluded that autogenous skin, both as a patch graft and as a free skin tube graft, will "take" and bridge the created defect in the esophagus (Fig. 1). The unhappy circumstance which followed was scar formation at the site of the skin tube graft, and strictures with extensive grafts. This, we felt, was a very serious problem. However, if controlled, skin tube grafts would be a real contribution to the field of esophageal surgery.

Substances which might delay and inhibit scar formation were logical things to try in an attempt to stop stricture formation at the operative site.

C. Piromen[2]†: An anti-inflammatory agent was used in five experiments with skin tube grafts. The regime using Piromen was 0.3 c.c. first day, 0.5 c.c. second day, 1.0 c.c. on the third day, and 1.0 c.c. daily thereafter.[3] All our animals died within the first week postoperative with the common finding of no healing of the graft. It could be lifted right out of its bed. We concluded that Piromen inhibits healing and prevents the skin tube from "taking."

From the Department of Gastro-Intestinal Research, Medical Research Institute of Michael Reese Hospital, Chicago, Ill.

This work was supported by AMA Grant No. 170 and American Cancer Society, Chicago Chapter. The Department is in part supported by the Michael Reese Research Foundation.

Read at the Thirty-sixth Annual Meeting of The American Association for Thoracic Surgery at Miami Beach, Fla., May 7 to 9, 1956.

*Department of Surgery (Thoracic), Michael Reese Hospital, Chicago Medical School, Cook County Hospital, Chicago, Ill.

†Supplied by Baxter Laboratories.

D. Reactive tissue tube: It was of great interest to us to note that in some animals where there was an esophageal leak, a reactive mediastinitis about the esophagus created a firm infiltrative wall. Perhaps, we thought, if a temporary tube would bridge the gap between the proximal and distal ends of cut esophagus long enough to produce a reactive wall, then a new channel might be

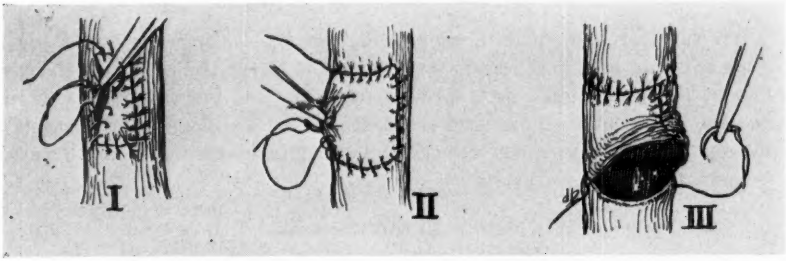


Fig. 1.—Autogenous skin grafts. *I*, Small patch. *II*, Large patch. *III*, Skin tube.

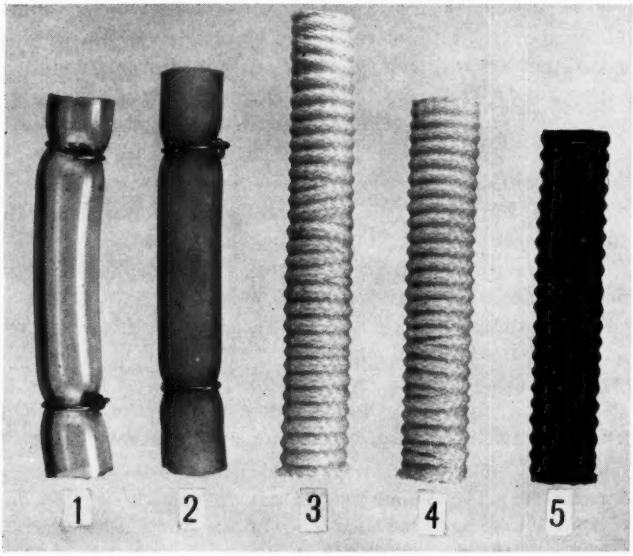


Fig. 2.—Prosthetic esophageal tubes used. *1*, Tygon untreated, nonreactive. *2*, Tygon treated with dicetyl phosphate, reactive. *3*, Crimped nylon tube, untreated. *4*, Crimped nylon tube sprayed with Krylon. *5*, Crimped nylon tube, shellacked.

created. Following the suggestion of Berman, a plastic tube (Tygon) was used in the thoracic esophagus.[4] However, in order to produce a severe tissue reaction, the tube was first impregnated with dicetyl phosphate[5] (Fig. 2, No. *2*), a drug which has been shown to cause severe inflammation with subsequent dense fibrous reaction.

Three experiments were performed in which such an impregnated Tygon tube was placed in the area of the pulmonary ligament between layers of

pleura. In each case within six to eight weeks a thin fibrous tissue tube was formed surrounding the plastic tube. These connective tissue tubes were used to bridge an esophagus defect and all led to fibrous stricture of the lumen within two to three weeks.

We knew that the connective tissue tube could be formed and that it could be used to bridge a defect in the esophagus. However, because of progressive fibrosis, this viable tube led to a stricture. Therefore, four experiments were done in which *reactive* Tygon tubing bridged the two ends of esophagus. The tubes were held in place by simple circumferential ties about the proximal and distal ends of the esophagus (Fig. 3, *A*). The stiff tube was to act as a support

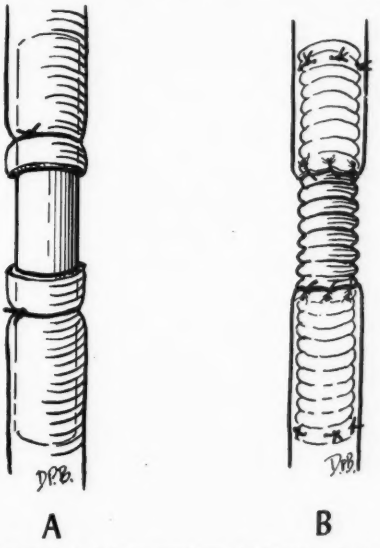


Fig. 3.—Sketch of technique used to bridge esophageal defects. *A*, Tygon tube held in place by circumferential ties. *B*, Crimped nylon tube held in place by interrupted stitches.

while a new connective tissue tube was forming about it. Our main problem encountered here was that the tube slipped. One dog lived four months before the tube slipped into the stomach. Within one week severe stenosis of the lumen followed. The other dog vomited the tube. In each case, stricture quickly ensued. Dilatations with graduated Hurst dilators were carried out successfully for two weeks on one dog. Through an error, subsequent dilatations were not done and again irreversible stenosis followed.

E. Crimped nylon tube prosthesis: The problem of better anchoring a prosthetic tube led us to try a crimped nylon tube.[6] (These tubes were described as vascular conduits by Edwards and Tapp.*) The advantage of the tube was its ability to take stitches and its semirigid flexibility. At first inspection it was seen that the tubes were not watertight and when moistened they were not

*We are obliged to Dr. J. S. Tapp of the Chemstrand Corporation for supply of these tubes.

firm. We therefore decided to stiffen and waterproof the tubes by two methods: (1) a water repellent spray (DuPont Krylon) was sprayed over the entire surface (see Fig. 2, No. *4*), and (2) the tube was placed in common shellac used in the physiology laboratory (see Fig. 2, No. *3*).

TECHNIQUE

The experiments were divided into replacement of segments of resected esophagus in two locations—the cervical esophagus and the thoracic esophagus. The technique for placing the tubes (see Fig. 3, *B*) was as follows: A 2-inch segment of esophagus was resected. Because of the elasticity of the organ, the gap between the proximal and distal ends was sometimes 3 inches. The nylon crimped prosthetic tube was inserted to bridge the defect. A general rule which we learned was that the portion of tubing which is to be inserted into the lumen of the esophagus must be the same length as the defect itself. That is, if the bridged area is 2 inches, then the portion of tube in the proximal and distal esophagus should be about 2 inches each. Hence, to bridge a 2- to 3-inch defect, the tube should be 6 to 8 inches long. Four to six interrupted cotton sutures are placed through the esophagus at each of the ends of the tube. This anchors the tube. The margins of cut esophagus are then sutured with interrupted stitches to the nylon tube. It is best to be able to pleuralize this area, if the mediastinal pleura is available. Care should be taken in the dissection of the esophagus to preserve its segmental blood supply.

Seven animals were operated on intrathoracically. Two dogs died of leakage and empyema in the first week postoperative. Two died of distemper within the first week postoperative, but the surgical site was intact. Three animals ate well for three to five weeks and then developed swallowing difficulties. In all the animals, the tube slipped out of the esophagus and into the stomach and, as in previous experiments, the new esophagus shrunk and strictured. It has always been our belief that these constricted areas could be dilated if they are recognized early enough. Because tubes slipped into the stomach without producing symptoms until the stricture of the esophagus was advanced, we decided to place the tubes in the cervical esophagus expecting the animal to vomit the tube when it became loose. Soon after the tube was vomited, dilatations could begin.

The cervical esophagus was exposed, and 1½- to 2-inch segments were removed. The defect was bridged as previously described. The dogs were placed on a rigid regime of nothing by mouth for seven days, atropine 7 mg., three times a day, to dry secretions, and intravenous fluids. This relatively simple procedure was successful in 5 dogs, who survived. In four to five weeks the tube was vomited and the new portion of esophagus began to contract. Dilatations can be successfully carried out if started early and maintained, first at daily, then at weekly intervals. For example (Dog No. 5413), the nylon tube was placed in the cervical esophagus. One week postoperatively the dog was eating well. A barium swallow three weeks later showed good swallowing, no obstruction, the prosthesis still in place. In four weeks the tube

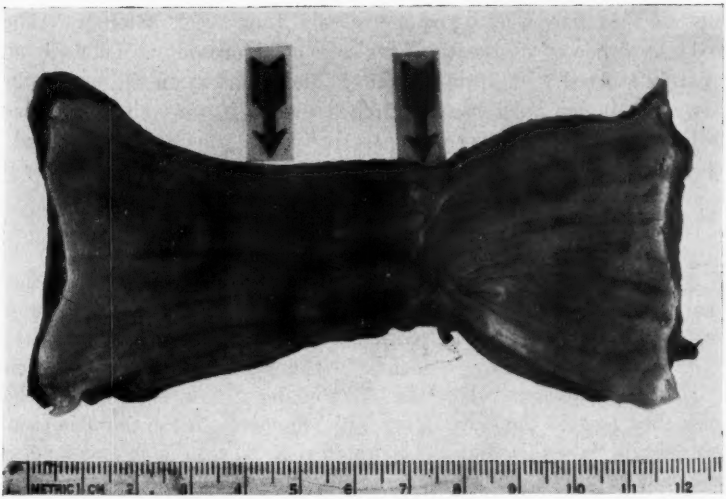


Fig. 4.—Dog No. 5413. Eight weeks postoperative sacrificed specimen. Area of substitute esophagus between arrows. Lumen adequately maintained by dilatations.

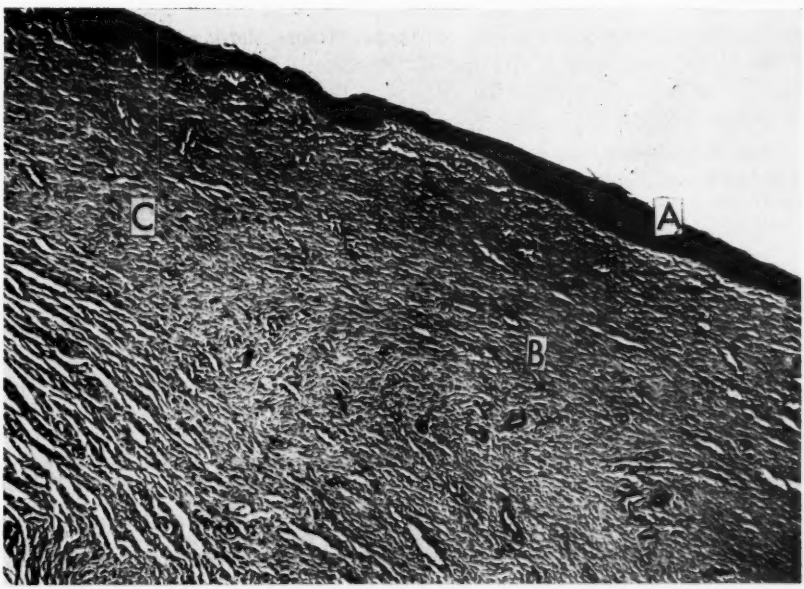


Fig. 5.—Microsection of specimen Fig. 4. *A*, Squamous-cell epithelium. *B*, Fibrous tissue wall of new esophagus. *C*, Normal esophagus.

was vomited. Progressive narrowing of the esophagus was noted on barium swallow so that five weeks postoperatively (one week after the tube was vomited), evidence of obstruction was seen on fluoroscopy. Dilatations were immediately started with Hurst mercury filled dilators on the unanesthetized animals. The lumen was easily stretched to No. 40 size, about the size of a thumb (Fig. 4). Eight weeks postoperatively, the animal was sacrificed. The new esophagus was lined with squamous-cell epithelium (Fig. 5). After dilatations the lumen is the size of a thumb (2.5 cm. in diameter).

DISCUSSION

It is evident that a new substitute esophagus can be created as was outlined. This new tube, however, has deficiencies. Namely, (1) it is not covered with muscle and it is not innervated, so that peristalsis is impaired, and (2) much more serious is the unfailing tendency of this structure to scar and contract. In the cervical esophagus, where the effort of deglutition is strong, the bolus is well propelled beyond the site of peristaltic absence. In the thoracic esophagus the bolus slowly passes through the operated site. The scarring and stricture can be controlled by use of dilators at frequent intervals. In the human being, who chews his food well, can complain of any early dysphagia, and who could cooperate, it is conceivable that this technique would be feasible, if associated with frequent dilatations.

It would seem that, if some technique could be developed which would prevent the stricture and scarring of the new tissue, the most serious handicap of this procedure would be eliminated. Another definite contribution (but perhaps not as favorable) would be to be able to place a prosthesis which would not leak and would not wander from its site.

Our experiments are proceeding in the two directions. We hope to be able to report further results.

CONCLUSIONS

1. Our experiences with substitute esophagus are related.
2. Substitute esophagus can be created.
3. The substitute esophagi created in the cervical esophagus are more successful and more easily maintained.
4. Stricture formation remains a major problem in the new tissue.

REFERENCES

1. Rubenstein, L. H., and Jefferson, N. C.: Repair of Experimental Esophageal Lesions With Skin Transplants, Surg. Forum, Am. Coll. Surgeons, Philadelphia, 1952, W. B. Saunders Co., vol. 1, p. 77.
2. Greene, L. C., Stuart, E. G., and Joraleman, J.: Survival Study of Thermally Injured Rats Treated With Piromen, Proc. Soc. Exper. Biol. & Med. **82**: 39, 1953.
3. Necheles, H., and Jefferson, N. C.: Personal communication.
4. Berman, E. F.: The Experimental Replacement of Portions of the Esophagus by a Plastic Tube, Ann. Surg. **135**: 388, 1952.
5. Abbott, O.: Discussion of a paper by Hollingsworth, Johnston, and McCooey: J. THORACIC SURG. **24**: 325, 1952.
6. Edwards, W. E., and Tapp, J. S.: Chemically Treated Nylon Tubes as Arterial Grafts, Surgery **38**: 61, 1955.

DISCUSSION

THORACIC SURGERY FORUM PAPERS

DR. ALFRED GOLDMAN, Beverly Hills, Calif.—I wish to direct my remarks to Paper No. 16, which has in it the problem of the acute pulmonary artery and right-sided heart occlusion, and I wish to demonstrate the physiologic effects of right-sided heart occlusion by occluding the pulmonary artery, with some observations we have made in a study of cinematography at the City of Hope Medical Center with Drs. Zeutlin, Rigler, Rehman, and Gyarfas. This work has so far been done only on dogs. In the course of these studies some observations have been made which shed light on what may happen after acute pulmonary artery occlusion. When the common pulmonary artery is occluded by a clamp, the right ventricle is seen to dilate, to increase its size, and the beat to become somewhat more feeble. If one is able to visualize what is going on within the right ventricular cavity, one sees that there is immediate dilatation of the atrioventricular valve, it becomes insufficient and there is a reflux of blood back into the venae cavae, and this is demonstrated in the movie. If one changes from a contrast medium such as Urokon or Diodrast to a contrast medium of a gaseous type, one can further study this problem. When this is done, if a mixture of helium and oxygen is used, injected at the rate of about 500 c.c. in less than two seconds, then the myocardium of the right ventricle appears different; it not only becomes markedly dilated, but also becomes red instead of cyanotic. There is no evidence of foaming within the right ventricle.

Motion picture—cinefluorography with electrocardiogram.

The right ventricle is cannulated and the dye will be injected into the right ventricle directly. The clamp is on the pulmonary artery, and you see the reflux, which has occurred through the insufficiency of the atrioventricular valve, opacifying both the superior and inferior venae cavae, with each ventricular systole. This of course is a visual demonstration of what we expect will happen.

After injecting helium 20 per cent and oxygen 80 per cent, the heart beats on as evidenced by the electrocardiogram. No foaming appears to occur although classically we think it should when there are large amounts of air in the right side of the heart. After five minutes the right heart has nearly filled with blood. The right ventricle is a deep red color, redder than the left, and apparently derives some oxygenation from the oxygen helium mixture. In another two minutes there is more blood and less gas, and after another injection there is actually some air reflux back through the tricuspid valve into the venae cavae. You can see the chordae tendineae, the valve action, and the dilated ring. After seven minutes no electrical changes occur and the heart is pumping regularly and all the gas has disappeared.

DR. H. HANSON, Stockholm, Sweden.—This discussion was not returned. EDITOR.

MR. DENNIS MELROSE, London, England.—This discussion was not returned. EDITOR.

DR. EARLE B. KAY, Cleveland, Ohio.—As you have gathered this morning, one is not considered very sociable in Cleveland unless he has a pump-oxygenator. I would like to describe the one Dr. Cross and I developed during the past year and to mention our technique for closure of ventricular septal defects.

(Slide) We have developed a rotating disc oxygenator-reservoir. It requires a minimum priming of 800 c.c. of blood but an optimum of 1,400 c.c. is used. The additional 600 c.c. act as a reservoir. Two sizes of oxygenators are used. One contains 60 and the other 100 Teflon discs. The smaller oxygenator has a capacity of 2,000 c.c. blood flow per minute and the larger has a capacity of 4,000 c.c. per minute. As the discs revolve, a thin film of blood is exposed to the oxygen in the upper part of the chamber.

(Slide) We have operated upon 17 patients with three deaths. There has been only one death in the last 11 patients, and that was a child with a severely malformed heart for which nothing could be done. We have utilized blood flows ranging from 40 to 80 c.c. per kilogram per minute, the majority having been between 60 to 70 c.c. per kilogram per minute. Flow rates have been dependent upon venous return and mean arterial pressure. Arterial oxygen saturations have varied from 97 to 103 volumes per cent. The average increase in hemolysis in the 17 patients was 32 mg. per cent. There was no significant trauma to the blood elements except for a slight fall in the platelet count as determined by phase microscopy. There was no bleeding tendency postoperatively. The average postoperative clotting time was seven minutes, which became normal within one or two hours. Cardiac by-pass times have ranged from fourteen to forty-five minutes.

Though hemolysis has not been a problem with the use of a Sigmamotor pump, experimentally we have found that this can be even further reduced by means of a hydraulic pump which compresses a large valved rubber tube through a fluid medium. This pump as demonstrated on the slide has a capacity ranging from 200 to 4,500 c.c. per minute.

(Slide) This is a photograph taken during closure of a large ventricular septal defect. If the sides of large defects are approximated by direct suture, there is a tendency for such sutures to pull out. Consequently, we utilize a plug of Ivalon sponge with multiple interrupted sutures. Since using this technique we have had only one patient who has had a murmur postoperatively. There have been no bundle branch blocks afterward. We feel that there is a certain advantage in maintaining the normal heartbeat (at least for most of the time) rather than stopping the heart, for it maintains a well-oxygenated myocardium; there has been no instance of ventricular fibrillation; it allows blood to escape through openings not completely closed so that additional sutures can be employed; and the flow of bright red blood will make other possible septal defects obvious. In 3 patients, multiple septal defects were present.

DR. DENTON A. COOLEY, Houston, Texas.—Our experience with extracorporeal circulation to the present time is limited to 6 patients with four survivors. The two deaths occurred in extremely sick infants with atrioventricular communis defects, one of which was probably completely uncorrectable. Four other cases of interventricular septal defects have all survived with gratifying results.

Our method of cardiac by-pass is similar to that described by Drs. DeWall, Read, and their associates with a bubble oxygenator and employing the reduced flow principle. Our heart-lung machine was constructed by Dr. Benjamin Belmonte.

Our experience is somewhat unique in that the survivors were all adults or adult-sized adolescents, and flow rates between 1,800 and 2,600 c.c. per minute were employed in an attempt to provide 40 c.c. per kilogram body weight per minute. Plasma hemoglobin in the oxygenated blood at the completion of the perfusion has not exceeded 50 mg. per cent and no ill effects have been demonstrated from hemolysis. Perhaps Dr. DeWall would comment on his own observations on hemolysis and other results of trauma to blood resulting from turbulence in the bubble oxygenator.

Unlike almost all other groups engaged in this type of work we have not used protamine to neutralize heparin following the perfusion and have observed no abnormal bleeding after operation. We have injected 1.2 mg. heparin per kilogram body weight just prior to the cannulation and the blood used for priming the oxygenator and pump contains 18 mg. heparin for each 500 c.c. blood. We have not used protamine because in 2 of our early

patients slow injections of even small amounts appeared to produce hypotension and we decided to determine the necessity for this drug after cardiac by-pass.

DR. WATTS R. WEBB, Jackson, Miss.—Many of the papers this morning have dealt with the dangers of ventricular fibrillation and various methods of controlling it or at least modifying it. This brings to mind that the exact mechanism of ventricular fibrillation is as yet incompletely understood, even though we do know many of the factors that help to control it. It is still highly debatable among cardiologists and physiologists whether it arises from a multifocal or from a unifocal site as a circus movement type of procedure. We have seen this morning that it can be regulated by many extraneous influences—drugs, electrolytes, and hormones. We have also heard from Dr. Shumacker's group that it can be regulated by factors influencing the auricular conduction system, that is, by blockade of the sinoauricular node and by dorsal sympathectomy. We have been blocking the atrioventricular node, either with procaine or by actually severing the conduction bundle in the region of the node. We have found that after either method with complete dissociation of the auricles and ventricles, it is quite difficult to produce fibrillation in the ventricle by an electric stimulus or by focal cooling. The exact significance of this remains uncertain. It seems to argue against the mechanism of ventricular fibrillation, from these types of stimuli at least, being due to a circus movement. It is believed that this will give us one more approach for studying the mechanisms and control of ventricular fibrillation.

DR. E. S. HURWITT, Scarsdale, N. Y.—I should like to comment briefly on Paper No. 18, in which Dr. Watkins demonstrated so nicely that myocardial irritability in hypothermic and normothermic dogs can be suppressed by the hormone-like preparation, somatotrophin. We were supplied with some of this drug, which was evaluated by the members of our anesthesiology department at the Montefiore Hospital in a group of normothermic human beings. Twenty-five noncardiac patients in regular sinus rhythm were prepared with this drug as Dr. Watkins described for the dog, given some twelve hours before and four hours before anesthesia. The myocardial irritability was registered by continuous electrocardiography during intratracheal intubation. Approximately one third of these patients demonstrated substantial evidence of myocardial irritability during intratracheal intubation. This was compared with a control group of patients prepared in exactly the same way, premedicated in the same way but without somatotrophin. One third of these patients also demonstrated substantial myocardial irritability. It was therefore our conclusion that in the normothermic human being, somatotrophin has no significant effect on suppressing myocardial irritability.

DR. CLARENCE W. LILLEHEI, Minneapolis, Minn.—In relationship to Dr. DeWall's presentation, the biochemical and physiologic responses in these first 80 patients to undergo total by-pass, utilizing the bubble oxygenator, have been studied in detail in order to acquire, if possible, a working knowledge of the numerous features unique to this field of surgery, since it has been readily apparent to us for some time that progress in this field of cardiac surgery has become possible largely through increased knowledge of physiologic mechanisms.

To date, at the University of Minnesota Hospitals, 144 patients have undergone a total by-pass procedure for various types of intracardiac lesions. These perfusions were performed by means of controlled cross circulation (45 patients), the arterial reservoir (5 patients), the biologic (dog lung) oxygenator (14 patients), and the artificial (bubble) oxygenator. This bubble-type oxygenator, consisting of a simple disposable unit sterilized by autoclaving, has been utilized for the last 80 intracardiac operations in infants, children, and adults. It is our expectation based upon this experience that this simple and efficient type of pump-oxygenator will accelerate the wide application of open intracardiac surgery in a manner comparable to the way in which the endotracheal tube accelerated the development of intrathoracic surgery.

After the initial learning phases of these operations, both the results and the risks of open heart surgery appear most closely related to certain patient factors. This will be brought out in a moment in the summary of our results with closure of ventricular septal defects.

(Slide) Fifty-three patients have had ventricular septal defects closed utilizing this pump-oxygenator, with thirteen deaths. These results are compared on this slide with the initial series of 27 patients similarly operated upon utilizing controlled cross circulation in which there were eight deaths. As we have emphasized before, controlled cross circulation serves as a most valuable standard for comparison since it constituted such an excellent physiologic method.

(Slide) Thus, among these 80 patients there were twenty-one deaths, and an analysis of the latter indicates that ten of these deaths occurred in the 25 infants under one year of age in whom closure was carried out. All these tiny infants had severe pulmonary hypertension and were rather desperately ill or they would not have been operated upon at that age.

One of the interesting aspects of this problem is the recognition by more and more physicians of the tremendous neonatal mortality of ventricular septal defects if left untreated surgically. In the past, of all patients dying with ventricular septal defects, one half have died before their first birthday.

Thus, there exists now a tremendous opportunity for the saving of life in this age group, and I hope that no one will misconstrue the fact that because the risk of treatment is higher in these tiny sick infants, surgical correction should not be attempted. In fact, quite the contrary should be true since the outcome otherwise is often inevitable. One of our deaths in the oxygenator series occurred in an 8-week-old infant who was operated upon as an emergency procedure in the middle of the night with only a clinical diagnosis of ventricular septal defect because our cardiologist deemed it unlikely that this infant could survive until the morning. The problems in such patients are largely concerned with the postoperative management of the complications occurring or existing in the damaged lungs, and this phase of management is constantly improving with experience.

(Slide) Here is an example of one such problem that is quite frequent in this age group. This preoperative chest roentgenogram is that of a 12-week-old infant with total collapse of the left lung due to compression of the left bronchus by the enlarged heart and pulmonary artery resulting from a ventricular septal defect.

(Slide) This little patient was operated on and is one of those fortunate ones that survived this serious situation. It was brought out yesterday in the discussion on congenital diaphragmatic hernias, and the same is true in these patients, that this compressed lung frequently is immature in these infants and when the intracardiac defect is repaired, even though the heart and the pulmonary artery become somewhat smaller, no amount of intrapulmonic pressure will expand that lung immediately. In fact, such attempts to expand it will only damage the good remaining lung. Such lungs may require several months' time before satisfactory aeration occurs.

(Slide) Finally, in the over-all group, taking in all age ranges the relationship to pulmonary resistance and pressures is an exceedingly important determinant of the risk of ventricular septal defect closure in a given patient. In those 51 patients of our series who had pulmonary hypertension that exceeded 80 per cent of their aortic pressures, there were nineteen deaths. In the 29 patients with elevated pulmonary pressures, but to less than 80 per cent of their systemic levels, there were but two deaths. Again I would emphasize that pulmonary hypertension is not, in my opinion, contraindication to reparative treatment because obviously those patients with the highest pressures are most desperately in need of help. The problem of reducing the risk for these unfortunate individuals, like all other problems, can be best solved by continuing to work at it.

DR. B. H. RAMSAY, Los Angeles.—I would like to briefly discuss Paper No. 26.

(Slide) Three years ago I presented a case of mucocele of the lung in a 17-year-old girl. This was noninfected; there was a septum present at the commencement of the segmental bronchus as illustrated. All the tributary branches were obstructed and filled with mucus. The failure of this clinical case to correspond with the experimental data presented today might have a ready explanation. The experimental work was done by obstructing the lobar bronchus and two things occurred. In the first place the lobe distal to

the obstruction underwent atelectasis. In the case presented here, the superior segment remained distended, apparently due to filling of the alveoli by collateral air drift. That might have distended the alveoli preventing entrance of mucus from the bronchi. Second, the smaller bronchi are less rigid in their walls and may distend and form cysts much more readily than a lobar bronchus with its many subdivisions. I would therefore await with interest an extension of the research which has been presented, and hope that similar experiments will be carried out where obstruction of the segmented and subsegmental bronchi is produced; and the other factor would be the prolongation of obstruction time from forty-eight weeks to perhaps even years to simulate clinical conditions.

DR. THOMAS J. O'NEILL, Philadelphia, Pa.—I should like to describe one slide and make one comment.

(Slide) This represents the pre- and postoperative x-ray findings on an 18-year-old boy who had anomalous venous drainage from the right lower lobe, a large tuberculous cavity occupying the right upper lobe, and anomalous drainage of the inferior vena cava emptying into the left atrium, and also a large interatrial septal defect. These defects were closed except for the lobectomy which will be done later. You can appreciate the remarkable difference in the redirection of these blood flows. This represents the fourteenth in a series of closure of interatrial septal defects. All were done by the closed or blind method and in no case was there an embolus, air or otherwise, no interference with cardiac action or blood flow, no operative mortality, and in no case was an extracorporeal machine used.

The comment I wish to make is that in this atmosphere of open surgery and many machines we ought to be somewhat discriminatory as to the area in which we use these machines.

DR. JOHN MAXWELL CHAMBERLAIN, New York, N. Y.—At the risk of being considered a social climber by Dr. Kay and the Cleveland groups, I would like to tell you about our pump-oxygenator. We have used as our oxygenator the animal's own lung. This concept is not new. The Minnesota group several years ago, at the Forum of the American College of Surgeons, presented a similar technique. However, they used only one lobe for oxygenation and we felt that an insufficient amount of blood was being oxygenated by this method. We have therefore used the entire left lung. Our technique is simply this: We have cannulated the superior and inferior venae cavae as Lillehei does, and blood from this source is conducted to a reservoir and then pumped into the ligated and cannulated left pulmonary artery. The oxygenated blood is then collected from the lung and passes again to a similar reservoir. The blood from the reservoir is then pumped back into the left subclavian artery.

(Slide) This is the twin pump that was developed by two engineers from the United Shoe Machinery Company in Beverly, Mass. It has many virtues; for example, it is extremely compact, small, portable, and quiet. Its outstanding virtue, however, is the hub micro-adjustment which lengthens and shortens the cam, thereby varying the amount of pressure on the tube which in turn determines the output of the pump. In other words, output is under complete control by this micro-adjustment at any moment.

(Slide) These are the twin reservoirs. The blood comes from the venae cavae to the reservoir on the left. It is then pumped back into the left pulmonary artery. The oxygenated blood returns to the reservoir on the right and is pumped back into the left subclavian. By keeping the blood in the reservoirs at the same level pulmonary edema has not occurred.

In this world of bubble oxygenators, membrane oxygenators, and film oxygenators, I hesitate to revive this old-fashioned method of oxygenating blood, but we feel that it still may have some practical value. At least, we hope this presentation will stimulate others to try it.

DR. J. L. EHRENHAFT, Iowa City, Iowa.—I would like to make a short comment on Paper No. 29, given by Dr. Higginson. We have had the opportunity to use an aortic

bifurcation homograft for substitution of the superior vena cava in a patient with benign mediastinal disease causing superior vena cava obstruction. The patient is a 34-year-old man who was admitted to the Veterans Hospital in Iowa City with the history of prominent veins over the upper portion of the thorax for the past six years. Four weeks prior to admission the patient developed a severe nonproductive cough and also some hoarseness. There was no hemoptysis. On physical examination the patient showed dilation of the superficial veins over the anterior upper chest and distention of the neck vessels. Venous pressure readings in the right arm were 290 mm. of water and in the left arm 310 mm. of water. Decholin circulation time was 25 seconds. The remainder of the investigation made us believe that this patient had a benign mediastinal granuloma and that we were not dealing with a malignant lesion. Bilateral angiograms with injection of the dye into both antecubital veins were performed and revealed obstruction of the superior vena cava.

On Jan. 5, 1956, a right thoracotomy was performed and the arterial homograft was inserted as you can see on this slide, by turning the graft upside down and anastomosing the common iliac vessels to the azygos and to the right innominate vein, respectively, and the aortic end of the graft was implanted into the superior vena cava intrapericardially after this vessel had been transected in this area. The patient did quite well postoperatively and showed definite improvement of the superior vena caval obstruction.

I would like to point out that in patients of this type it is very important that venograms be obtained from both sides to delineate the site of obstruction of the superior vena cava. Sometimes those obstructions extend into the innominate veins and are not localized to the superior vena cava alone. We feel that this type of treatment is of definite benefit in patients who have benign lesions. I do not feel that this type of procedure should be done in patients with carcinoma of the lung or other malignant lesions producing obstruction of the superior vena cava. Patients with malignant lesions producing this symptom are usually quite well managed with nitrogen mustard and irradiation therapy.

DR. RALPH A. DETERLING, JR., New York, N. Y.—I wish to congratulate Dr. Higginson on his aggressive approach to the problem of superior vena caval obstruction and on his good results. In a recently published report, we collected 8 case reports from the literature in which vessel replacement had been carried out for superior vena caval obstruction. We also reported a personal case in which the patient has now had a satisfactorily functioning homograft in the superior vena cava for two and one-half years. Her obstruction was due to a calcified tuberculous lymph node situated at the level of the azygos vein. It was interesting to us that the clinical results with aortic homografts were as good or better than those achieved with autogenous veins.

Our experimental work in dogs with various types of replacements for the superior vena cava was for the most part discouraging, especially with the use of several types of synthetic fabrics as well as Ivalon sponge. Only about 30 per cent remained patent. We were also surprised at the poor results with the use of autogenous vein grafts. It was our thought that a continuous suture line might be partly to blame, but subsequent implantations employing interrupted sutures did not improve the results. Interestingly enough, our experimental use of preserved aortic homografts in the vena cava was encouraging, contrary to the experience of some others, and I believe that I would employ such a graft again in the future. It should be pointed out that implantations into the auricle or the appendage apparently become occluded by thrombosis much more readily than if the replacement is made only in the vena cava.

In closing, I would point out that symptomatology in some cases with partial or complete superior vena caval obstruction is not severe enough to warrant exploration in every case. In other patients in whom advanced malignant involvement is found at exploration there might be some question in certain instances as to whether one is justified in treating the caval occlusion at all. I would agree with Dr. Higginson that if such an implantation could be performed simply, the patient's comfort might be greatly enhanced even though the ultimate outcome in unaffected.

DR. ROLLINS HANLON, St. Louis, Mo.—I should like to discuss Dr. Higginson's paper. We have been concerned by the possibility of delayed obliteration in arterial homograft substitution for the superior vena cava, and have searched for a more satisfactory subtsitute. A limited experience with Ivalon prostheses in replacing the superior vena cava in dogs has been disappointing. Venous autografts have been used in 2 patients with benign obliteration of the superior vena cava. In one of these, the internal jugular vein was interposed as a free graft between the left innominate vein and the intrapericardial portion of the superior vena cava, with the distal end of the right subclavian vein anastomosed into the side of the graft. A good clinical result has been maintained for more than a year. In the second patient, the superficial femoral veins were employed as autografts between the innominate veins and the intrapericardial vena cava. Evidence of venous hypertension has disappeared but the patient has been followed for only a month. Further trial seems warranted to test the long-term efficacy of venous autografts, which have important theoretical advantages.

DR. FRANK S. ASHBURN, Washington, D. C.—I too want to discuss Dr. Higginson's paper. Recently we have had occasion to treat a case of superior vena caval obstruction by the use of a graft. This case, as well as the experimental work done by Drs. Huggins and Sewell in the Naval Research Institute, is to be published soon in THE JOURNAL OF THORACIC SURGERY. The one point I wanted to make is that it seems to make a difference whether or not the stump of the superior vena cava is used for the anastomosis, or whether the end of the graft is merely put into the auricle itself or into the auricular appendage.

(Slide) When the stump of the superior vena cava was used in the dogs for the anastomosis of the graft, no stricture occurred, but whenever the graft was put into the auricle or into the auricular appendage, routinely, this diaphragm-like obstruction occurred and the dogs all developed evidence of superior vena caval obstruction. It would seem, then, if possible, that it would be advisable to use the stump of the superior vena cava each time this procedure is done.

DR. CLARENCE DENNIS, Pelham Manor, N. Y.—My associates and I have been concerned with the problem of artificial heart-lung devices since 1947. In the 9 patients we have perfused since the first unsuccessful one was done in 1951, we have been inclined to feel that our animal work has been confirmed, especially with regard to the titration of our heparinization throughout the procedure. Having found such titrations contributory to success during these years, while nearly all other groups have found titration to be too cumbersome or unnecessary, it is very gratifying to listen to Mr. Hurt's presentation this morning. Our protamine titration method was set up either late in 1949 or early in 1950 by Dr. Russell Nelson, whom you have heard this morning; he was a member of the group at that time.

The following factors suggest the wisdom of precise monitoring of the degree of heparinization: (1) there is a variation in the potency of different lots of protamine; (2) there is excessive bleeding if an overdose of protamine is given; (3) the protamine effect is apparently less prolonged than the heparin effect, and heparin is destroyed by the body over the time the perfusion is in progress; and (4) there are variations in the susceptibility of different individuals to given amounts of protamine or heparin administration.

Therefore, since the spring of 1950, we have followed routinely a course which I will outline, including the first 2 patients perfused in 1951. First, we use protamine titrations routinely, essentially as Mr. Hurt has described them; (2) we govern the heparin addition to the donor reservoir in each perfusion by protamine titration, ordinarily succeeding in getting a concentation of 40 to 50 mcg. of heparin per millimeter of blood; and (3) we repeat the titration every thirty minutes during perfusion and every hour after the end of perfusion to maintain levels of less than 5 mcg. per millimeter so as to avoid additional bleeding.

With regard to the shocklike state and the oozing tendency, both seem to be on the basis of vasodilatation, and both seem, in our laboratory at least, to be avoided by diluting the protamine somewhat and infusing it slowly over fifteen-minute periods. With these precautions, coagulation has ceased to be a problem with us, either in the laboratory or on clinical patients whom we have perfused.

DR. ALFRED HURWITZ, Brooklyn, N. Y.—I rise to discuss Dr. Higginson's paper which was so admirably presented. Dr. Adrian Kantrowitz and I have employed Dacron grafts to by-pass the superior vena cava in 6 dogs. Dr. Deterling had previously reported failure because of thrombosis with tubular Dacron grafts that he had employed in dogs. In an attempt to eliminate stenosis and secondary thrombosis at the site of anastomosis between the graft and the right auricular appendage, we made the graft in the form of a truncated cone. The wider end of the graft was sutured to the appendage. Even with this modification, 5 dogs underwent complete thrombosis and the sixth dog showed marked stenosis.

(Slide) This angiogram reveals the bête noire of the operation, namely, the formation of a thrombus in the graft at the site of anastomosis with the auricular appendage. The graft is completely occluded and an extensive collateral circulation has become manifest. In conclusion, until we can use materials with a greater degree of nonwettability, it would be advisable to use freeze-dried arterial homografts to by-pass thrombosed veins.

DR. PAUL NEMIR, JR., Philadelphia, Pa.—I wish to thank the discussants for their comments. I was interested in Dr. Goldman's remarks. We have been impressed with the paucity of signs and symptoms following complete occlusion of either the right or left pulmonary artery. Actually, except for the occasional case having an elevation of the main pulmonary artery pressure following occlusion of either the right or left branch, there have been no other untoward effects. In no case have we seen a picture which would simulate that which follows a pulmonary embolus. It became increasingly apparent as the study progressed, that complete occlusion of a main branch of the pulmonary artery in the unanesthetized patient, with the peri-arterial nerve fibers intact and with the lung in situ, produced in no respect the profound changes which occurred with pulmonary embolism. Studies on pulmonary embolism are in progress in our laboratory. In addition to the arterial blockade which occurs in pulmonary embolism, it seems likely that neurogenic reflexes are set up which play a major role in this catastrophe. We have injected certain substances distal to the occluding balloon under strictest possible control with the hope that we might selectively reproduce, at least in part, certain of the findings generally observed with pulmonary embolism. The substances which we have injected so far have been histamine and 5-hydroxytryptamine or serotonin. In the amounts which we have used and by the methods used, we obtained, in no case, a picture which could be considered similar to that of pulmonary embolism.

I wish particularly to thank Dr. Hanson for his comments. Dr. Hanson and his associates in Stockholm developed this method of study and we are indebted to them for many helpful suggestions and comments. They have had, by far, the largest experience with this method of study and with their excellent radiographic techniques they have widely applied it in the study of lung function, lung physiology, and pulmonary anatomy.

Erratum

In the article entitled "Early Complications Following Resection for Pulmonary Tuberculosis" by DR. DAVID V. PECORA, which appeared in the August issue of the JOURNAL, pages 216-225, the last sentence of the text on page 216 should read as follows: "Pyrazinamide and viomycin were also given to selected patients whose organisms were resistant to other drugs."

Announcements

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Notice of Annual Meeting

The Thirty-seventh Annual Meeting of The American Association for Thoracic Surgery will be held May 4, 6, and 7, 1957, in Chicago, Illinois. Headquarters will be at the Palmer House.

Requests for Hotel Reservations

These should be mailed directly to Mr. Edward Langford, Reservations Manager, Palmer House, Chicago. Please mention this Association, the type of accommodation desired, the date, and approximate hour of arrival and departure. If accommodations are desired elsewhere in Chicago, please communicate directly with the hotel of your choice.

Thoracic Surgery Forum

The Thoracic Surgery Forum will be continued as a special session at the 1957 meeting. The Forum is primarily for the presentation of short papers on current thoracic research, experimental problems, anatomical studies, and modified or new surgical techniques. The inclusion of any considerable amount of clinical material in these reports makes the choice more difficult and the Program Committee reserves the right to reject such papers, or to suggest their transferal to the Regular Program.

Papers at this session will be limited to ten minutes, including the showing of lantern slides or other illustrative material. At the discretion of the President, three minutes may be allowed as the maximum discussion for each paper.

All Thoracic Surgery Forum papers will be published together in one issue of the JOURNAL. Maximum length: 3000 words without illustrations. If illustrated, an appropriate number of words must be subtracted for each cut used.

Abstracts of Papers

Abstracts of all papers for presentation at the 1957 meeting must be received on or before Dec. 15, 1956, otherwise they will not be considered by the Program Committee.

Abstracts should be labeled "For Thoracic Surgery Forum," or "For Regular Program." The abstracts should contain from 200 to 250 words and accurately reflect the contents of the completed paper.

With regard to the shocklike state and the oozing tendency, both seem to be on the basis of vasodilatation, and both seem, in our laboratory at least, to be avoided by diluting the protamine somewhat and infusing it slowly over fifteen-minute periods. With these precautions, coagulation has ceased to be a problem with us, either in the laboratory or on clinical patients whom we have perfused.

DR. ALFRED HURWITZ, Brooklyn, N. Y.—I rise to discuss Dr. Higginson's paper which was so admirably presented. Dr. Adrian Kantrowitz and I have employed Dacron grafts to by-pass the superior vena cava in 6 dogs. Dr. Deterling had previously reported failure because of thrombosis with tubular Dacron grafts that he had employed in dogs. In an attempt to eliminate stenosis and secondary thrombosis at the site of anastomosis between the graft and the right auricular appendage, we made the graft in the form of a truncated cone. The wider end of the graft was sutured to the appendage. Even with this modification, 5 dogs underwent complete thrombosis and the sixth dog showed marked stenosis.

(Slide) This angiogram reveals the bête noire of the operation, namely, the formation of a thrombus in the graft at the site of anastomosis with the auricular appendage. The graft is completely occluded and an extensive collateral circulation has become manifest. In conclusion, until we can use materials with a greater degree of nonwettability, it would be advisable to use freeze-dried arterial homografts to by-pass thrombosed veins.

DR. PAUL NEMIR, JR., Philadelphia, Pa.—I wish to thank the discussants for their comments. I was interested in Dr. Goldman's remarks. We have been impressed with the paucity of signs and symptoms following complete occlusion of either the right or left pulmonary artery. Actually, except for the occasional case having an elevation of the main pulmonary artery pressure following occlusion of either the right or left branch, there have been no other untoward effects. In no case have we seen a picture which would simulate that which follows a pulmonary embolus. It became increasingly apparent as the study progressed, that complete occlusion of a main branch of the pulmonary artery in the unanesthetized patient, with the peri-arterial nerve fibers intact and with the lung in situ, produced in no respect the profound changes which occurred with pulmonary embolism. Studies on pulmonary embolism are in progress in our laboratory. In addition to the arterial blockade which occurs in pulmonary embolism, it seems likely that neurogenic reflexes are set up which play a major role in this catastrophe. We have injected certain substances distal to the occluding balloon under strictest possible control with the hope that we might selectively reproduce, at least in part, certain of the findings generally observed with pulmonary embolism. The substances which we have injected so far have been histamine and 5-hydroxytryptamine or serotonin. In the amounts which we have used and by the methods used, we obtained, in no case, a picture which could be considered similar to that of pulmonary embolism.

I wish particularly to thank Dr. Hanson for his comments. Dr. Hanson and his associates in Stockholm developed this method of study and we are indebted to them for many helpful suggestions and comments. They have had, by far, the largest experience with this method of study and with their excellent radiographic techniques they have widely applied it in the study of lung function, lung physiology, and pulmonary anatomy.

Erratum

In the article entitled "Early Complications Following Resection for Pulmonary Tuberculosis" by DR. DAVID V. PECORA, which appeared in the August issue of the JOURNAL, pages 216-225, the last sentence of the text on page 216 should read as follows: "Pyrazinamide and viomycin were also given to selected patients whose organisms were resistant to other drugs."

Announcements

THE AMERICAN ASSOCIATION FOR THORACIC SURGERY

Notice of Annual Meeting

The Thirty-seventh Annual Meeting of The American Association for Thoracic Surgery will be held May 4, 6, and 7, 1957, in Chicago, Illinois. Headquarters will be at the Palmer House.

Requests for Hotel Reservations

These should be mailed directly to Mr. Edward Langford, Reservations Manager, Palmer House, Chicago. Please mention this Association, the type of accommodation desired, the date, and approximate hour of arrival and departure. If accommodations are desired elsewhere in Chicago, please communicate directly with the hotel of your choice.

Thoracic Surgery Forum

The Thoracic Surgery Forum will be continued as a special session at the 1957 meeting. The Forum is primarily for the presentation of short papers on current thoracic research, experimental problems, anatomical studies, and modified or new surgical techniques. The inclusion of any considerable amount of clinical material in these reports makes the choice more difficult and the Program Committee reserves the right to reject such papers, or to suggest their transferal to the Regular Program.

Papers at this session will be limited to ten minutes, including the showing of lantern slides or other illustrative material. At the discretion of the President, three minutes may be allowed as the maximum discussion for each paper.

All Thoracic Surgery Forum papers will be published together in one issue of the JOURNAL. Maximum length: 3000 words without illustrations. If illustrated, an appropriate number of words must be subtracted for each cut used.

Abstracts of Papers

Abstracts of all papers for presentation at the 1957 meeting must be received on or before Dec. 15, 1956, otherwise they will not be considered by the Program Committee.

Abstracts should be labeled "For Thoracic Surgery Forum," or "For Regular Program." The abstracts should contain from 200 to 250 words and accurately reflect the contents of the completed paper.

Five, repeat, five copies of *each* abstract must be sent to Miss Ada Hanvey, Administrative Assistant, The American Association for Thoracic Surgery, 600 South Kingshighway, St. Louis 10, Missouri.

Those on the program are reminded that papers presented at the meeting *must* be handed to the secretary immediately after their presentation. If they are not ready at that time there is a chance that they will not be published in THE JOURNAL OF THORACIC SURGERY.

Motion Picture Session

Provisions have been made to show a limited number of motion pictures to be selected on a competitive basis. *The films themselves,* together with descriptive material concerning length of presentation, etc., must be received by Dr. Karl P. Klassen, The Ohio State University, Columbus 10, Ohio, before Dec. 15, 1956.

It is planned to run the motion pictures in a smaller room at the same time as the scientific sessions. If the films are well labeled, it will not be necessary for the author to be present for comment.

Applications for Membership

Applications for Associate Membership in the Association must be received by the Membership Committee not later than Dec. 15, 1956, otherwise the application will be deferred for consideration until the 1958 meeting.

Applicants must be sponsored by three Active or Senior Members of the Association. In addition to the signatures on the application form, the sponsors will forward a *separate* letter concerning the applicant directly to:

Dr. O. T. Clagett
Chairman of the Membership Committee
Mayo Clinic
Rochester, Minn.

Sponsors are reminded that *new* letters of recommendation must be forwarded to the Membership Committee should their applicants be held over for reconsideration a second year. The new letters of recommendation should also be sent to Dr. Clagett, the Chairman of the Membership Committee.